Diabetic Foot

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ABSTRACT

According to the 1998 National Health Survey, diabetes mellitus now affects 9.0% of Singaporeans aged between 18 to 69 years[72]. There are many associated complications such as hypertension, arteriosclerosis, hyperlipidemia, ischaemic heart disease, cerebrovascular accidents, retinopathy, nephropathy, as well as peripheral neuropathy of which contributes to ulceration on the foot. Among the above, one of the most common complication in the lower extremities is diabetic foot ulcer. It is estimated that 15% of diabetic patients will develop an ulcer in the lower extremities some time during the course of their illness[36, 77, 81].

In this paper, we will discuss the pathophysiology, complications, and treatment of diabetic foot ulceration and infection. Several clinical case studies have been provided in the hope that they can be a window to the overall view of the different treatment modalities.

PATHOPHYSIOLOGY OF DIABETIC FOOT ULCER

The pathogenesis of diabetic foot ulcer and subsequent infection is a complex interplay between three major processes: neuropathy, angiopathy, and immunopathy. Other putative factors involved in the diabetic foot syndrome include limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity[1, 14, 37, 57, 70, 71, 81, 83, 98]. Peripheral neuropathy in diabetes mellitus is likely due to altered nerve metabolism resulting from chronic hyperglycemia[10]. Sensory neuropathy, motor neuropathy and autosympathectomy oftentimes act in synergy to result in diabetic foot ulceration.

Sensory neuropathy i.e. loss of pain and temperature sensation predisposes the involved area to repeated traumas such as burns, abrasions, or mechanical stresses. Loss of pain sensation is probably the primary cause of ulceration of the diabetic foot[11, 17, 78]. Patients with loss of protective sensation are unable to feel a 10-gram (Semmes-Weinstein 5.07) nylon filament and are considered at risk of ulceration because they are unable to protect their feet from injury[9, 46, 74, 89].

Motor neuropathy weakens the intrinsic muscles of the foot; this leads to the development of foot deformities such as foot drop, equines, hammertoes, and prominent plantar metatarsal heads[12, 32, 48, 86]. Such deformities cause altered weightbearing distribution[29].

Autosympathectomy results in dry skin, cracking, and fissuring; a portal of entry for infection is thus created[33, 86]. Autosympathectomy also causes dilation of the arteries and arterioles thus increasing blood flow to the foot[7, 28, 30]. Associated with this condition is arteriovenous shunting which reduces capillary flow. This increases tissues' susceptibility to injury, slow tissue healing and reduced tissue resistance to infection[97].

Angiopathy can be divided into 2 categories: macroangiopathy and microangiopathy.

Diabetes is one of the most important risk factors for peripheral vascular disease. Atherosclerosis presents as a more diffuse disease, with more multisegmental involvement and compromised collateral circulation. Peripheral vascular disease predisposes a diabetic patient to ulceration and possible infection secondary to ischemic skin changes. Lack of oxygenation and difficulty in delivering antibiotics to the site of infection also impair resolution of any infections.

LoGerfo noted arteriolar or microcirculatory occlusive process is not involved in microangiopathy[22, 92]. Non-occlusive abnormalities in the microcirculation of diabetics, typically capillary basement membrane thickening, may cause transcapillary leakage of albumin, and limited white blood cell migration[66, 67]. Decreased leukocyte migration would reduce resistance to infection[30, 68].

Diabetic patients with poor glucose control are predisposed to infection[80]. Impaired cell-mediated immunity seems to be the major contributor to immunopathy and subsequent development of infection[25]. In the presence of hyperglycemia, phagocytosis and the intracellular killing function of the leukocytes appear to be significantly altered[8, 27]. Infection as an additional mechanism of injury of the foot has been described by Brand[15, 17]. Infected exudates are pushed deeper as patients who are insensate to pain continue to walk on the infected foot.[16]

Neuropathic osteoarthropathy, also known as Charcot's arthropathy, is a common complication in diabetics with severe neuropathy. It is characterized by joint dislocation, pathologic fractures and severe pedal architectural destruction. Neuropathic osteoarthropathy is a complex disorder involving neurovascular and musculoskeletal systems. Autosympathectomy of the vasculature and arteriovenous shunting increases the resting blood flow in patients with neuropathic osteoarthropathy dramatically.

This high flow rate results in osteopenia. Multiple small mechanical insults unrecognized by the patient that occur in the osteopenic bone cause bony dissolution and loss of structural integrity, eventually resulting in collapse deformity. The primary risk factors for neuropathic osteoarthropathy are severe peripheral sensory neuropathy, normal circulation, and a history of preceding trauma, often

minor in nature. Clinically, the foot is warm, swollen, non-tender, and strikingly deformed.

COMPLICATIONS OF DIABETIC FOOT

- **Amputation**

Amputation is a feared complication of diabetic foot ulcers. Studies have shown that the rates of lower extremity amputation in diabetic patients are 15-40 times higher than those found in persons without diabetes[4, 34, 36, 57, 81, 84]. There are many factors that contribute to an increased risk of lower extremity amputation.

Peripheral vascular disease is one of the significant independent risk factor for amputation[2, 32, 37, 78, 81, 83, 86]. This condition can also bring about an increased risk of gangrene which may indirectly lead to the need for amputation. Hence, it is crucial that arterial insufficiency be detected early for timely vascular intervention to take place so as to avoid amputation[3, 19].

Infection has also been shown to increase the risk of amputation[81, 83]. Due to the poor wound healing, systemic sepsis as well as the ongoing infection, there can be widespread necrosis of the tissues and the resulting gangrene may necessitate amputation to remove all infected material [3, 19, 32] and avoid further proximal loss of the limb. Clinical features will include soft tissue infection with severe loss of tissue, abscess formation as well as osteomyelitis.

Chronic hyperglycemia has been postulated to be one of the risk factor for amputation[47, 59, 60, 73, 76, 82, 88]. This factor has been shown, in many studies, to be associated with a range of other diabetic complications such as microangiopathy, peripheral neuropathy, impaired phagocytosis by the leucocytes and glycosylation of tissue proteins[4, 5, 6].

All above attribute significantly to ulcer formation, poor wound healing and eventually may result in amputation. Other co-morbidities related to diabetes mellitus such as retinopathy, nephropathy and cardiovascular factors have been shown to be linked with amputation as well[13, 44, 70]. A past history of amputation is a good predictor of amputation as it increases the risk for further ulcer formation with secondary infection and thereby leading to amputation[2, 14, 44, 55]. The rate of ulcer recurrence has been shown to be higher in patients who had previous amputation. Following amputation, it is believed that the plantar pressures are unevenly distributed and the osseous architecture is altered and hence leading to recurrent ulcer formation on the foot. In the case of re-amputation, it is usually due to disease progression, poorly healing lesions, as well as the presence of other risk factors for amputation that had developed from the first amputation.

- **Infection**

Infections in diabetic patients are more common and severe than in non-diabetic patients. Studies have documented that infections in diabetic foot are usually caused by more than one microbe which may include skin commensals[3, 19, 38, 39, 41, 65]. The infecting organisms are dependent on the patient's local environment and the nature of initial injury. The common infecting microbes are gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus*, enteric aerobic gram-negative rods such as *E.coli* and *Enterobacter* and anaerobes (e.g. *Bacteroides fragilis*). Any breach in the skin layer will allow bacteria microbes to infiltrate and infect the tissues. Once infection has occurred, many factors such as hyperglycaemia, poor immune responses by the body, peripheral neuropathy and peripheral vascular disease may further contribute to infections which can be limb-threatening. Poor vascular supply to the lower limb will affect the delivery of antibiotics to the infection site and hyperglycemia which is seen in poorly controlled diabetes will impair the ability of the leucocytes to kill the bacterial pathogens. Infections are allowed to develop and spread, resulting in vast and irreversible tissue damage[19]. Sensory neuropathy contributes to further progression of infection as a result of continued use of the foot as well as delay in detection[77].

CLASSIFICATION OF DIABETIC FOOT ULCERS

In the Wagner classification, lesions of diabetic foot ulcers are broadly classified into 6 grades which are based on the depth of penetration, the presence of complications such as osteomyelitis or gangrene and the extent of tissue necrosis[9] (Table 1).

Table 1. *Wagner Classification*

Classification	Characteristics
Grade 0	Skin is intact. There may be multiple calluses, deformities and bony prominences present which will give rise to a "foot at risk".
Grade 1	A localized and superficial ulcer whose base may be clean or purulent and it does not extend beyond the skin layer.
Grade 2	An ulcer which extends deep into the tendon, bone, ligament and joint. The base of the ulcer may be clean or purulent.
Grade 3	The lesion extends further to form an abscess and is complicated by osteomyelitis.
Grade 4	Gangrene of the toes or the forefoot is present.
Grade 5	Severe gangrene of the foot and a below knee amputation may be required.

Treatment

Treatment is complicated by the systemic nature of diabetes and it is best rendered by a multidisciplinary team consisting of a dietician, endocrinologist, infectious disease specialist, vascular surgeon, orthopedic surgeon, diabetic nursing specialist, orthotist, prosthetist, and podiatrist.

- **Patient Education**

Prevention rather than seeking to cure diabetic foot ulcers when they arise is the best approach socially and economically. Good patient education will come a long way to minimize such problems and a patient who is well educated in this aspect can play a more active and responsible role in the care of their own feet. Hence, patients with diabetes mellitus should understand the condition, its complications as well as the need for good glycaemic control. It is crucial that instructions given to

patients are clear and concise for ease of comprehension. However, we need to consider our local culture before giving practical advice. For example, slippers are greatly preferred to shoes in our local population but they are not ideal for diabetic patients. This is because the exposed areas of the foot are at increased risk of injury. Advice to wear covered shoes, both within the home and outside, to protect their feet and prevent ulcer formation should be emphasized. Other suggestions to care for the diabetic foot will include daily washing of the feet to keep them clean, the need for early medical consultation for early diabetic foot lesions as well as to visually check their shoes and feet and feel for points of excessive pressure that may lead to ulcer formation due to peripheral neuropathy.

- **Debridement**

Ulcers will not heal in the presence of nonviable tissue and debris. It is thus imperative to debride necrotic tissue in the treatment of diabetic foot ulcers. Adequate debridement must always to done before applying topical wound healing agents, dressings, or wound closure procedures[58, 62, 90].

Among the various types of debridement, surgical debridement is the only method proven efficacious in clinical trials[90]. All nonviable soft tissue and bone from the open wound is accomplished primarily with a scalpel, tissue nippers, and/or curettes. Necrotic tissue must be excised as deeply as necessary until healthy, bleeding soft tissue and bone are encountered. Callus tissue surrounding the ulcer necessitates removal. A diabetic ulcer associated with a deep abscess requires hospital admission and immediate incision and drainage. In the presence of osteomyelitis, joint infection, or gangrene, joint resection or amputation of the foot may be needed. The rate of wound healing can be hastened by removal of necrotic tissue on a regular basis[90, 91].

- **Off-loading**

Reducing pressure to the diabetic foot ulcer so as to prevent continual trauma is necessary for treatment[3, 19, 20, 21, 70]. The patient's physical characteristics, compliance with treatment, and the location and severity of the ulcer are all determinants of the choice of off-loading modality. Some examples of off-loading techniques useful in the management of diabetic foot ulcers are:

- Total non-weight bearing: crutches, bed rest, wheelchair
- Total cast contact [53, 54, 75]
- Patellar tendon –bearing braces
- Half shoes or wedge shoes
- Removable walking braces with rocker bottom soles
- Foot casts or boots [18, 45]
- Healing sandal – surgical shoe with molded plastizole insole [33, 35]
- Accommodative dressings: felt, foam, felted-foam, etc, [33, 43, 85]

Total contact casts are minimally padded, well-molded plaster casts that allow even distribution of pressure across the plantar surface of the foot, so as to eliminate the excessive concentration of pressure responsible for the ulceration. It also helps to immobilize and rest the foot. Compliance is not an issue because patients are unable to remove the casts.

Total contact cast may be used for any localized forefoot ulcer 3 cm or less in diameter with good pedal pulses. In general, if there is vascular insufficiency or infection, a total contact cast is contraindicated.

- **Wound Management**

A moist wound environment bandaged to protect it from trauma and local contamination can facilitate healing process. Size, depth, location, and the wound surface of the ulcer are factors for consideration in selecting the type of dressing. Normal sterile saline are often used and considered as a standard for wound care.

Chronic ulcers may benefit from autologous platelet releasates, recombinant DNA platelet-derived growth factor (becaplermin), tissue-engineered human dermal replacement (Dermagraft ®), and human skin equivalent (Apligraf ®). Efficacy for many other treatment modalities for chronic wound has not been clearly demonstrated and more supporting studies are needed.

- **Management of Infection**

Unattended infection can threaten both limb & life. Presence of infection must be identified and determined as local, ascending and/or systemic. In the evaluation of the patient, his/her current medications and prior antibiotic use may interfere with planned treatments or indicate that standard treatments are likely to be ineffective.

Diabetic foot infection can be classified as limb-threatening or non-limb-threatening. In non-limb-threatening infections, the ulceration is usually superficial, does not extend to any bone or joint, and there is no accompanying ischemia. However, some patients may present with cellulitis without ulceration due to infection from small puncture wounds, scratches, and simple fissures. This cellulitis is 2 cm or less from the portal of entry. Systemic involvement is usually absent. Non-limb-threatening infections are relatively mild and management is usually on an outpatient basis with appropriate antibiotic therapy, wound management, pressure reduction, and patient education[3, 19, 39]. Hospitalization with intravenous antibiotics should be considered if improvement is unsatisfactory.

If cellulitis extends greater than 2 cm, the infection is classified as limb-threatening[39]. Other features may include lymphangiitis, soft tissue necrosis, fluctuance, odor, gangrene, abscess, necrotizing fasciitis and/or osteomyelitis. The infection or ulcer may probe into bones, joints, sinus tracts, or tendon sheaths. If bone is exposed, the patient is assumed to have osteomyelitis until proven otherwise[41, 42]. Fever, chills, loss of appetite and/or malaise may be evidence of systemic toxicity. However, up to half of these patients may present with no systemic symptoms or leukocytosis due to immunosuppresion from diabetes. Unexplained or recalcitrant hyperglycemia is frequently the only indication of infection[39]. Hospitalization should be considered mandatory.

Vascular status must be assessed and consultation for potential revascularization is required to prevent limb amputation[3]. Reliable anaerobic and aerobic cultures should

be obtained from pus or curettage of the ulcer base to aid antibiotic therapy. Plain-film X-rays may be used to look for the presence of bony erosions and/or gas in the soft tissues. It is noteworthy that the demonstration of osteomyelitis by X-rays lags the onset of bone involvement by 10-14 days[64, 69].

Radionuclide bone scans such as Tc99 may demonstrate abnormal uptake of the radionuclide before changes can be observed on X-rays[50]. As MRI has higher tissue contrast and ability to detect both soft tissue and marrow inflammation, it has generally supplanted the CT scan in the early diagnosis of osteomyelitis[64]. The patient's nutritional and metabolic status must be assessed and properly maintained as such relatively common abnormalities in these patients can impair wound healing and resolution of infection[26, 61]. Other laboratory tests might include full blood count with or without differentials, blood cultures, glycosylated haemoglobin, fasting blood sugar, sedimentation rate, and urinalysis.

Infection is usually polymicrobial, with a variety of gram-positive cocci, gram-negative rods, and anaerobic organisms predominating. Empirical antibiotic therapy includes broad-spectrum coverage for more common isolates from each of these three categories.

Initial antibiotic therapy may be adjusted to provide more specific coverage once the wound culture results have been obtained. In chronically treated diabetic foot ulcer patients, methicillin-resistant staphylococci have been emerging as important pathogens[93]. Early detection and treatment can avoid further tissue loss or extension of infection.

Early surgical treatment including simple debridement of the soft tissues, wide incision and drainage of the pedal compartments, or open amputation to eliminate extensive areas of infection is typically necessary. When gangrene or extensive tissue loss is present, early amputation at the appropriate level may be necessary to remove the focus of infection and to attain viable tissue margins[39,65]. The ultimate goal for the patient is restoration and maintenance of function and independence.

For osteomyelitis, resection of infected bone with or without local amputation and concurrent antibiotic therapy is the optimal management[63]. The infection may be treated as a soft tissue infection after the affected bone has been completely resected or amputated. However, if residual infected bone remains in the wound, 4 to 8 weeks of antibiotic therapy based on the culture results will be needed.

- **Vascular Intervention**

Surgical re-vascularization can improve the outcome of diabetic foot ulcerations and infections if significant peripheral vascular disease is detected. This is so even in the presence of microangiopathy. Vascular studies are thus importance in the evaluation of the foot.

Ankle brachial index is a good predictor of wound healing. Normal values are > 1.0 and values < 0.4 denote critical limb ischemia and surgical re-vascularization may be helpful in preventing amputation. Calcification of vessels in diabetic patients may falsely elevate ankle brachial index; using toe brachial index may give a more accurate picture. A normal toe brachial index is > 0.6 If these evaluations demonstrate ischemia, contrast angiography is required to plan the surgical re-vascularization. Arterial re-vascularization is performed once after ongoing infection, if present, has resolved. Direct arterial reconstruction is frequently required. The fundamental goal of re-vascularization is to re-establish pulsatile arterial flow to the infected foot[23]. After successful restoration of arterial perfusion to the foot, secondary procedures for definitive treatment of the foot lesion may be undertaken. Further debridement or amputation may be necessary; skin grafting of well-granulating tissue can also be considered.

The use of surgical re-vascularization for the treatment of limb-threatening ischemia has become a highly successful means of limb salvage. Diabetics who present with limb-threatening ischemia may have multiple levels of arterial occlusion; re-vascularization of each level is necessary to achieve wound healing and limb salvage.

Transluminal angioplasty of iliac artery stenoses may be combined with lower extremity bypass to restore arterial flow to the foot.

- **Surgical Intervention**

In Ray amputation, the toe and its corresponding metatarsal bone is removed. Any combination of toes and their corresponding metatarsals can be removed. However, it is recommended that not more than one Ray should be removed as the patient will find difficulties fitting into shoes and may risk developing late equines. Central Ray excisions are at an increased risk of poor wound healing. 1st and 5th ray excisions tend to function well in normal shoes. In the excision of the 1st ray, the length of the metatarsal is preserved to the greatest extent to allow for effective restoration of the medial arch and gait can be well-compensated in a rocker-bottom shoe. Removal of the lateral Rays, leaving the first metatarsal bone and great toe intact, usually leaves a well-functioning foot.

In transmetatarsal amputation, the incision occurs at the level of the necks of the metatarsals. It begins medially and laterally at the mid-thickness of the foot and it goes straight down to the bone. The outer edges of the 1st and the 5th metatarsals and the plantar aspect of the shaft of the other metatarsals are beveled to reduce the pressure concentration of the soft tissues. If the 2nd and the 3rd metatarsals are of a longer length than the others, pressure areas may form when the patient is allowed to resume normal activity. This procedure is usually carried out when removal of single or multiple toes are not possible. The ischaemic index should be at least 0.45 in the mid-foot. The ulcer or gangrene should not extend too proximally into the mid-foot such that the flap will not be viable.

In Syme amputation, the remaining limb is a partial foot as the heel of the foot is present. Together with the leg, the heel pad will allow for better functioning as compared to a below-knee amputation. However, the ankle or foot is not mobile.

It is usually carried out in two stages because forefoot infection will usually lead to the presence of residual bacteria. Briefly, in the first stage, ankle disarticulation takes place to remove the infected forefoot and in the second stage, the malleoli is removed and subsequently the stump is shaped. The skin of the heel pad should not have any open

lesions. Doppler ischemic index at the ankle should be 0.45 or more. It is important to note that this method of amputation will fail if the posterior tibial artery is completely occluded. This form of amputation is usually indicated in infection and gangrene of the forefoot and transmetatarsal or tarsal amputation is not possible.

Below knee amputation is usually carried out at the level of the junction of the proximal third and the middle third of the calf to the mid-calf. The distal third is often not considered because of the soft tissue padding at this level is insufficient and its relative avascularity. The length of the stump in adults often ranges from 12.5 to 17.5cm.

Other forms of amputations such as above knee amputation may be carried out at times and the choice depends on a range of factors such as the ischaemic index of the lower limb.

- **Management of Neuropathic Osteoarthropathy**

The central tenets of care for neuropathic osteoarthropathy are offloading, stabilization and protection from further trauma. In the acute inflammatory stage, the foot is immobilized in a non-weightbearing cast until resolution of inflammation. This process may take months. If a deformity or instability cannot be effectively controlled or accommodated by prescription footwear or bracing, reconstructive surgery may be considered. The extreme hyperemia, osteopenia, and edema during the acute stage of the disease make surgery inadvisable. Most operations for neuropathic osteoarthropathy consist of exostectomies for "rocker-bottom" deformities. Complex arthrodesis procedures such as isolated or multiple midfoot fusions, triple arthrodeses, tibio-calcaneal, and ankle fusions are increasingly popular. Offloading is still necessary post-operatively. Careful patient selection and management is important because amputation can be an unwanted complication of failed surgical procedures

- **Hyperbaric Oxygen Therapy**

Hyperbaric oxygen therapy (HBO) is defined as a mode of management where the patient is allowed to breathe 100% oxygen in a chamber where the pressure is 2 to 3 atmospheres absolute (ATA). Oxygen is being transported in the blood either chemically by binding to the hemoglobin molecules in erythrocytes or physically by dissolving in the plasma in accordance to Henry's law[94]. As such, a significant proportion of the arterial oxygen will be in dissolved form in the plasma at a pressure greater than one atmosphere and hence tissues are exposed to greater concentrations of oxygen than normal would permit[51]. In addition, HBO has been noted, in many studies, to promote neovascularisation[87] and increase endothelial cells, fibroblast proliferation[95] and collagen deposition[49]. Moreover, it can alter the functions of the activated neutrophils l eading to decreased adhesions between the neutrophils and endothelial surfaces as well as an increased oxidative microbial killing[52]. This therapy can be carried out in either a monoplace or a multiplace chamber. Generally, HBO is well tolerated and most of the adverse effects such as middle ear barotraumas, sinus squeeze and myopia are mild and reversible while severe ones are rare[24, 40, 79]. This therapy is absolutely contraindicated in untreated pneumothorax as well as concurrent administration of chemotherapeutic agents and disulfiram.

Case Studies

- **Case 1 (Figure 1)**

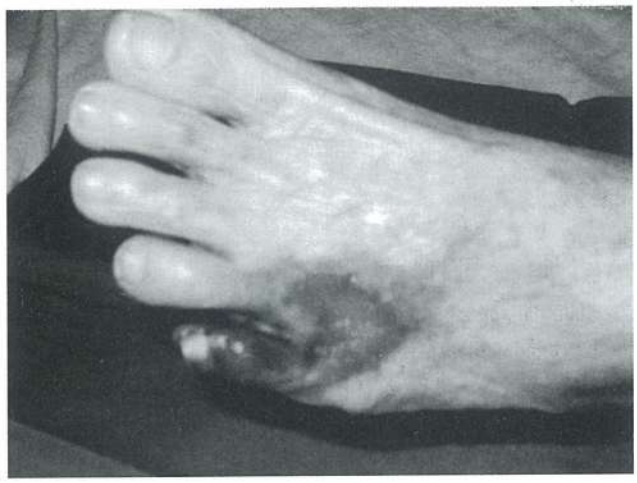

Figure 1. Case 1. Wet gangrene of the 5th toe extending proximally to the level of the web space. Wagner Grade 4.

WCN is a 87-year-old Chinese lady who was residing in an old folks' home. She had multiple co-morbidities such as diabetes mellitus, stroke, atrial fibrillation and hypertension. She had diabetes mellitus for 30 years and admitted poor compliance to medication. For this hospital admission, she presented with a 3 week history of non-healing ulcer over the left little toe which was gradually turning black. The patient could not specify any precipitating traumatic event. There was no previous such episode. She was unaware that foot ulceration could be a complication of diabetes mellitus.

On examination, her left 5th toe was reddish black in colour and this extends to the level of the web space. There is a 3 cm wide, superficial ulcer over the dorsum of the foot between the 4th and the 5th metatarsals. Slough was noted at the base of the ulcer and there was purulent discharge seen as well. Although the nails were noted to be healthy, the surrounding skin appeared inflamed.

As there was wet gangrene over the 5th toe which appeared to be extending proximally, her ulcer was classified under grade 4 according to Wagner classification Her skin was dry and several fissures could be seen. There were no obvious deformities in the foot noted. There was reduced sensation up to the mid-shin level bilaterally. The dorsalis pedis, posterior tibial and the popliteal pulses were absent bilaterally. Otherwise, patient was systematically well.

The clinical diagnosis of diabetic foot was made and several investigations were performed. She was unable to feel a 10-gram monofilament as assessed by the podiatrist. Culture of the wound sample showed mixed growth of gram-negative bacilli predominated by *Pseudomonas aeruginosa*. Ultrasound Doppler arterial left lower limb showed occlusion at multiple sites such as external iliac common artery, superficial femoral artery, anterior and posterior tibial artery. Ankle brachial index measurements for her right and left limbs were 0.10 and 0.08 respectively, signifying severe arterial obstruction. Abnormalities were

also found for toe brachial index measurements; 0.06 and 0.08 for left first and second toe respectively and 0.08 for both right first and second toe.

There was no radiological evidence of osteomyelitis or air within soft tissue.

Patient education is de rigueur for all patients who present with diabetic foot ulcers and/or infection. This is especially so for first presentation of diabetic ulcer, as is this case. The aforementioned advices should be taught to her by all members of the health care team with the doctor playing the leadership role.

Surgical debridement may be carried out for her to remove all necrotic and non-viable tissue and bone. Antibiotic treatment should be started for her at the same time to prevent bacteraemia and possible systemic sepsis which is highly probable at her age. She is not suitable for vascular intervention as her ankle brachial index revealed severe arterial obstruction with values <0.4 bilaterally. Unfortunately, we have to recommend below knee amputation for her as blood flow is only reasonable and tissue healing is optimal at this level. Medical and social rehabilitation in the form of prosthesis fitting and counseling should also be carried out to allay fears and improve functional status post-operatively

- **Case 2 (Figure 2)**

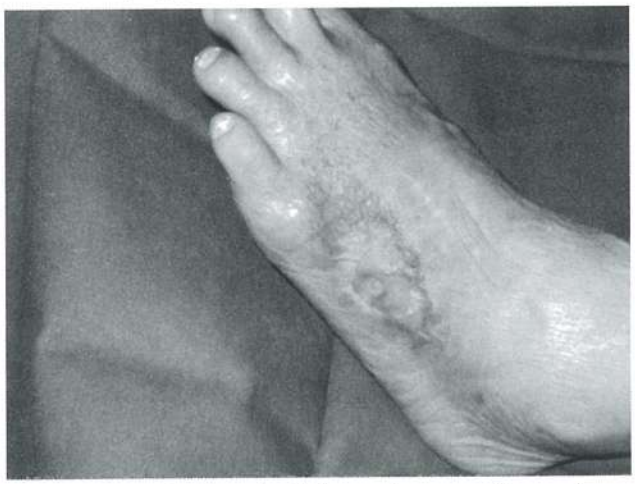

Figure 2. Case 2. Superficial ulcer with surrounding erythema. Wagner Grade 1.

HT, a 72-year old Chinese lady, with a significant history of diabetic mellitus. She defaulted medication for the past one month and complained of a non-healing, painful ulcer over the left foot for a duration of 3 days.

On examination, there was a 3 cm wide ulcer over the dorsolateral aspect of the left foot. At the base of the ulcer, there was no slough or purulent discharge observed. However, there was 2.5cm wide rim of erythema in the surrounding skin.

The ulcer was superficial and no complications such as abscess and gangrene were present, hence the ulcer was classified under Wagner grade 1.

There was dermopathy noted over both lower limbs. There were no obvious deformities in the foot noted. Sensation was reduced up to the ankles bilaterally. The dorsalis pedis and posterior tibial pulses were absent bilaterally. Otherwise, the patient was systematically well.

The clinical diagnosis of diabetic foot was made and several investigations were performed. The ankle brachial index measurements were normal with a value of 1.45 bilaterally. The toe brachial index measurements were abnormal at the 1st and the 2nd toe bilaterally. There was no radiological evidence of osteomyelitis or air within soft tissue.

Culture of the swab from the lesion revealed mixed growth of gram-negative organism including skin commensals such as Staphylococcus aureus and Group B streptococci.

We would first like to stabilize her glucose levels to prevent possible complications. Once her systemic condition is optimized, specific attention can be directed to the ulcer on her foot. Again, we would start her on broad spectrum intravenous antibiotics and narrow it when the culture results are returned. Surgical debridement would be necessary for both diagnostic and therapeutic purposes. Since vascular studies of her lower limbs were optimal, any surgical intervention need not be considered at this present moment. Lastly, we should not forget to educate her regarding her current condition and how she can contribute positively to her health.

- **Case 3 (Figure 3)**

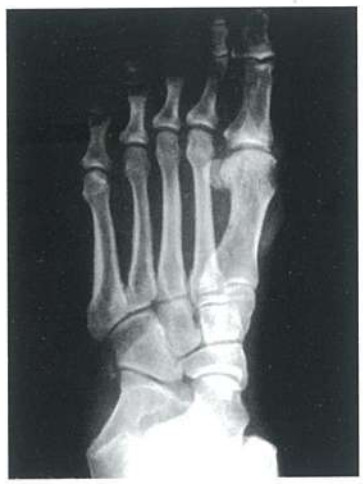

Figure 3. Case 3. Osteomyelitic changes seen in the head of the 1st metatarsal bone (Xray). Wagner Grade 3.

LES, a 75-year-old gentleman who has long-standing diabetes mellitus for 38 years presented with a painful non-healing ulcer over the left foot of 3 weeks duration. On examination, there was 2.5 cm wide ulcer over the plantar aspect of the first metatarsal head of the left foot. There was a purulent discharge noted from the edge of the ulcer. The ulcer extended beyond the subcutaneous layer into the bone. The surrounding skin was also noted to be erythematous.

Diabetic dermopathy was noted over both lower limbs. However, there were no obvious deformities seen. Sensation was poor up to the knee bilaterally. The dorsalis pedis artery and the posterior tibial artery were absent on the left side. However, all distal pulses were present over the right side except posterior tibial artery. Otherwise, the patient was systemically well.

The clinical diagnosis of diabetic foot was made and several investigations were performed. The ankle brachial index measurement over the left side was 0.54 and the right side was 0.88. The toe brachial index measurements were

0.42 for the left and 0.99 for the right. Osteomyelitic changes can be observed in the X-ray of the left foot. The ulcer was thus classified Wagner grade 3.

Culture of the sample tissue taken from the wound site revealed mixed growth of gram negative bacilli namely *Enterobacter* and *Bacteroides Fragilis*.

Once again, patient education is the starting point for treatment plan. Surgical debridement should be carried out for him as soon as possible to remove necrotic tissue to avoid further complications. He should be started on intravenous broad spectrum antibiotics as there is a high possibility of bacterial infection. The choice of antibiotic should be altered accordingly when culture results are out. As osteomyelitic changes were observed in the X-ray, we would consider carrying out Ray amputation of the 1st left toe.

- **Case 4 (Figure 4)**

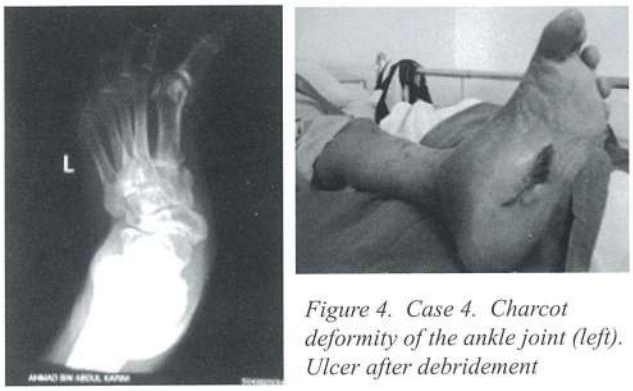

Figure 4. Case 4. Charcot deformity of the ankle joint (left). Ulcer after debridement

Ahmad is a 59-year-old Malay gentleman who was admitted for an infected left plantar diabetic ulcer. He had multiple co morbidities such as diabetes mellitus for 30 years, hypertension, and ischemic heart disease. He had the ulcer for a week and it was painful although he was still ambulating. He could not recall any trauma, cuts or insect bite to the area.

On examination, there was a 4 cm superficial ulcer over the plantar aspect of his foot. Cellulitis was observed in the surrounding skin extending for 3 cm around the ulcer. There was no slough at the base of the ulcer, but there was purulent discharge.

Of note, there was neuropathic osteoarthropathy in the left foot. Sensation of both legs was lost up to the mid-shin level. Distal pulses were weak in the left foot and absent in the left. No systemic abnormality.

Clinical diagnosis was that of infected left plantar diabetic ulcer and several investigations were performed. Wound culture showed mixed growth of gram-negative organisms including skin commensals and Group B streptococcus, Pseudomonas aeruginosa, and Peptostreptococcus species. Ultrasound Doppler arterial left lower limb showed occlusion of the mid-segment of the posterior tibial artery.

Ankle brachial indices for his right and left limbs were 0.52 and 0.32 respectively. Toe brachial indices were 0.23 and 0.56 for his right first and second toes respectively; 0.08 and 0.13 for her left first and second toes respectively. There was no radiological evidence of osteomyelitis or air within soft tissue.

Patient education, systemic diabetes, antibiotic treatment and surgical debridement should be managed as per previous cases. After the resolution of his infection, vascular intervention and treatment on his Charcot foot should commence. Vascular intervention such as angioplasty or vascular bypass will improve wound healing time and prevent recurrence. The Charcot foot which is in the acute inflammatory phase should be immobilized nonweightbearing in a total contact cast. Immobilization may have to be continued for 4-6 months until inflammation become quiescent. Surgery may be advised as aforementioned. Thereafter, the patient may be referred to the podiatrist for supportive measures.

- **Case 5**

NLK is a 42-year-old Chinese lady who has long standing diabetes mellitus complicated by peripheral neuropathy and retinopathy. Other co-morbidities include hypertension, ischemia heart disease, and hyperlipidemia. She has had several amputations done, dating back to 1999 when she had Ray's amputation of her left big toe and right little toe. She underwent Ray's amputation again two months ago for her right fourth toe due to infected ulcer with osteomyelitis. She is currently admitted for swelling of the right third toe and fever for duration of three days.

Upon examination, there was a 1 cm ulcer over the plantar aspect of her right third toe. Her right third toe was swollen and erythematous. There was foul-smelling purulent discharge. The ulcer was classified under Wagner grade 1 as it was superficial and no abscess, gangrene or osteomyelitis was present.

Diabetic dermopathy was observed over the shin bilaterally. Of note, the patient has neuropathic osteoarthropathy of her ankle joints bilaterally. She has loss of sensation of all modalities up to the mid-shin level bilaterally. Pulses of both feet were felt and capillary refill was less than two seconds. She was slightly febrile, otherwise there was no other abnormal findings systematically.

The clinical diagnosis of diabetic foot complicated by Charcot's joint with infected right third toe ulceration was made and several investigations were performed. Of note, wound culture showed mixed growth of gram-negative organisms including skin commensals and Group B streptococcus and Staphylococcus aureus. There was no radiological evidence of osteomyelitis or air within the soft tissue.

As she suffers from recurrent ulceration, patient education is not to be overlooked. She does not control her eating habits; the doctor and dietician will have to inculcate in her the suitable diet for her to control her blood sugar levels. Chronic hyperglycemia can increase risks of diabetic foot infections.

As the ulcer is primarily neuropathic, local debridement and offloading may be helpful. The optimal offloading device would be a total contact cast. When the ulcer starts showing appreciable improvement, foot care can be gradually simplified with prefabricated walking braces, and then healing shoes.

Careful evaluation of her recurring ulcer is necessary. As her ulcers were all in the forefoot, the increased forefoot loading she may be experiencing can be treated with

percutaneous Achilles tendon lengthening followed by immobilization in a below-knee walking cast for 4-6 weeks.

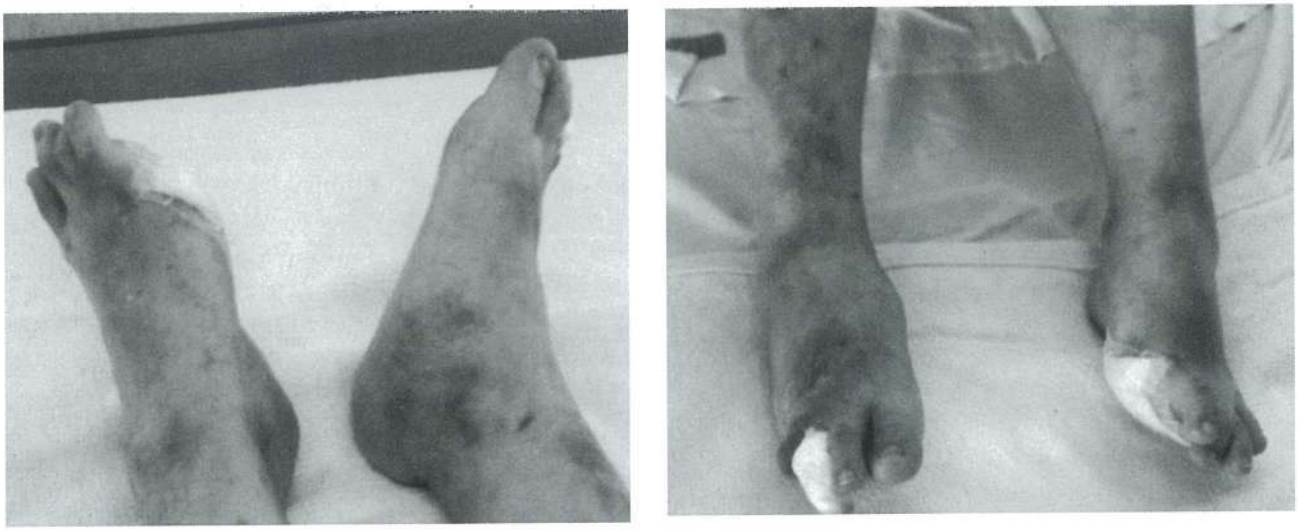

Figure 5. Case 5. Charcot deformity of the right ankle joint. The 1st toe of the right foot and the left 4th and 5th toes have been amputated. Diabetic dermopathy has been noted bilaterally as well (right).

CONCLUSIONS

The management of diabetic patients poses many challenges. Among the most significant is the treatment of diabetic foot ulcer, infection and/or gangrene. These conditions result from several factors; including but not exclusively, neuropathy, angiopathy and immunopathy. Ulceration, infection, gangrene and lower extremity amputation take a tremendous toll on the physical, mental, and functional well-being to the patient. Although all diabetic foot complications cannot be absolutely prevented, reducing their incidence through appropriate management and prevention programs is indeed achievable.

With the increasing knowledge of the pathophysiology behind the diabetic foot; the advent of new products in wound care such as Becaplermin, Apligraf, and Dermagraft; lighter and better fitting prostheses that can decrease the metabolic demand of walking; and other biomedical advancements, the treatment of diabetic foot ulceration and its complications is continually evolving. Although these will pose a challenge to the healthcare team in meting out the optimal treatment plan for each individual patient, prognosis for these patients will definite be more optimistic.

REFERENCES

1. Abbott, C.A., Vileikyte, L., Williamson, S., Carrington, A.L., Boulton, A.J.M. Multicenter study of the incidence and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 21:1071–1075, 1998.
2. Adler, A.I., Boyko, E.J., Ahroni, J., Smith, D.G. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 22:1029–1035, 1999.
3. American Diabetes Association. Consensus development conference on diabetic foot wound care. Diabetes Care 22:1354–1360, 1999.
4. American Diabetes Association. Diabetes 1996 Vital Statistics. American Diabetes Association, Alexandria, VA, 1996.
5. American Diabetes Association. Implications of the Diabetes Control and Complications Trial. Diabetes Care 23 (Suppl. 1):S24–S26, 2000.
6. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care 23(Suppl. 1):S27–S31, 2000.
7. Archer AG, Roberts VC, Watkins PJ. Blood flow patterns in painful diabetic neuropathy. Diabetologia 1 984;27:563-567.
8. Bagdade JD, Root RK Bulger RD. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes 1974;23:9-15.
9. Birke JA, Sims DS. Plantar sensory thresholds in the insensitive foot. Leprosy Review 1988; 57 :26 1-267
10. Boulton AJM. Diabetic neuropathy. In: Frykberg RG (ed). The high-risk foot in diabetes mellitus. Churchill Livingstone, New York 1991:49-59.
11. Boulton AJM, Hardisty CA, Betts RP, et al. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. Diabetes Care 1983;6:26-33.
12. Boulton, A.J., Meneses, P., Ennis, W.J. Diabetic foot ulcers. A framework for prevention and care. Wound Rep. Reg. 7:7–17, 1999.
13. Boulton, A.J.M. The pathway to ulceration. In: The Foot in Diabetes, 3rded., pp. 19–31, edited by A.J.M. Boulton, H. Connor, and P.R. Cavanagh, John Wiley & Sons, Chichester, UK, 2000.
14. Boyko, E.J., Ahroni, J.H., Stensel, V., Forsberg, R.C., Davignon, D.R., Smith, D.G. A prospective study of risk factors for diabetic foot ulcer: The Seattle Diabetic Foot Study. Diabetes Care 22:1036–1042, 1999.
15. Brand PW. Repetitive stress in the development of diabetic foot ulcers. In: Levin ME, O'Neil LW (eds). The Diabetic Foot, ed 4. Mosby, St. Louis, Mo. 1988:83-90.
16. Brand PW: the diabetic foot. In: Ellenburg M, Rifkin H (eds). Diabetes mellitus: theory and practice, ed 3. Medical Examination Publishing Co. Inc., New Hyde Park, N.Y. 1983:829-849.
17. Brand PW. The insensitive foot (including leprosy). In: Jahss MH (ed). Disorders of the foot. WB Saunders Co., Philadelphia 1982:vol.2.
18. Burden, A.C., Jones, G.R., Jones, R., Blandford, R.L. Use of the Scotchcast boot in treating diabetic foot ulcers. Br.Med. J. 286:1555, 1983.

19. Caputo, G.M., Cavanagh, P.R., Ulbrecht, J.S., Gibbons, G.W., Karchmer, A.W. Assessment and management of foot disease in patients with diabetes. N. Engl. J. Med. 331:854–860, 1994.
20. Catanzariti, A.R., Haverstock, B.D., Grossman, J.P., Mendocino, R.W. Off-loading techniques in the treatment of diabetic plantar neuropathic foot ulceration. Adv. Wound Care 12:452–45, 1999.
21. Cavanagh, P.R., Ulbrecht, J.S., Caputo, G.M. What the practising physician should know about diabetic foot biomechanics. In: The Foot in Diabetes, 3rd ed., pp. 33–59, edited by A.J.M. Boulton, H. Connor, P.R. Cavanagh, John Wiley & Sons, Chichester, UK, 2000.
22. Conrad MC. Large and small artery occlusion in diabetics and nondiabetics with severe vascular disease. Circulation 1967;36:83-91.
23. C.M. Akbari and F.W. LoGerfo, Diabetes and peripheral vascular disease. J Vasc Surg 30 (1999)
24. Davis JC, Dunn JM, Heimbach RD. Indications for hyperbaric oxygen therapy. Tex Med 1980;76:44-7
25. Delbridge L, Ctercteko G, Fowler C. Reeve TS, Le Quesne LP. The aetiology of diabetic neuropathic ulceration of the foot. British Journal of Surgery 1985;72:1-6.
26. Dickhaut, S.C., DeLee, J.C., Page, C.P. Nutritional status: importance in predicting wound healing after an amputation. J. Bone Joint Surg. 66-A:71–75, 1984.
27. Dolkart RE, Halpern B, Perlman J. Comparison of antibody response in normal and alloxan diabetic mice. Diabetes 1971;20:162-7. 28. Edmonds ME, Clark MD. Newton S. et al. Increased uptake of bone radiopharmaceutical in diabetic neuropathy. Quarterly Journal of Medicine 1985;572:843-855.
29. Edmonds ME. The diabetic foot: pathophysiology and treatment. Clinical Endocrinological Metabolism 1986; 15:889-916.
30. Edmonds ME. The neuropathic foot in diabetes: part 1. Blood flow. Diabetic Medicine 1986;3: 111-15.
31. Flynn, M.D., Tooke, J.E. Aetiology of diabetic foot ulceration: a role for the microcirculation? Diabetic Med. 8:320–329, 1992.
32. Frykberg, R.G. Diabetic foot ulcers: current concepts. J. Foot Ankle Surg. 37:440–446, 1998.
33. Frykberg, R.G. Diabetic foot ulcerations. In: The High Risk Foot in Diabetes Mellitus, p. 151, edited by R.G. Frykberg, Churchill Livingstone, New York, 1991.
34. Frykberg, R.G. Epidemiology of the diabetic foot: ulcerations and amputations. Adv. Wound Care 12:139–141, 1999.
35. Frykberg, R.G. Podiatric problems in diabetes. In: Management of Diabetic Foot Problems, 2nd ed., p. 66–87, edited by G.P. Kozak, D.R. Campbell, R.G. Frykberg, and G.M. Habershaw, WB Saunders, Philadelphia, 1995.
36. Frykberg, R.G., Habershaw, G.M., Chrzan, J.S. Epidemiology of the diabetic foot:ulcerations and amputations. In: Contemporary Endocrinology: Clinical Management of Diabetic Neuropathy, p. 273, edited by A Veves, Humana Press, Totowa, NJ, 1998
37. Frykberg, R.G., Lavery, L., Pham, H., Harvey, C., Harkless, L.,Veves, A. Role of neuropathy and high foot pressures in diabetic foot ulceration. Diabetes Care 21:1714–1719, 1998.
38. Frykberg, R.G., Veves, A. Diabetic foot infections. Diabetes/Metab. Rev. 12:255–270, 1996.
39. Gibbons, G.W., Eliopoulos, G.M. Infection of the diabetic foot. In: Management of Diabetic Foot Problems, p. 121, edited by G.P. Kozak, D.R. Campbell, R.G. Frykberg, and G.M. Habershaw, WB Saunders, Philadelphia, 1995.
40. Giebfried JW, Lawson W, Briller HF. Complications of hyperbaric oxygen in the treatment of head and neck disease. Otolaryngol Head Neck Surg 1986;94:508-12
41. Grayson, M.L. Diabetic foot infections. antimicrobial therapy. Infect. Dis. Clin. North Am. 9:143–161, 1995.
42. Grayson, M.L., Gibbons, G.W., Balogh, K., Levin, E., Karchmer, A.W. Probing to bone in infected pedal ulcers: a clinical sign of underlying osteomyelitis in diabetic patients. JAMA 273:721–723, 1995
43. Guzman, B., Fisher, G., Palladino, S.J., Stavosky, J.W. Pressure-removing strategies in neuropathic ulcer therapy. Clin. Podiatr. Med. Surg. 11:339–353, 1994.
44. Harris, M.I. Diabetes in America: epidemiology and scope of the problem. Diabetes Care 21(Suppl. 3):C11–C14, 1998.
45. Hissink, R.J., Manning, H.A., van Baal, J.G. The MABAL shoe, an alternative method in contact casting for the treatment of neuropathic diabetic foot ulcers. Foot Ankle Int. 21:320–323, 2000.
46. Holewski ii, Stess RM, Graf PM, et al. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. Journal of Rehabilitation Residual Development 1988;25:1-10.
47. Humphrey, A., Dowse, G., Thoma, K., Zimmet, P. Diabetes and nontraumatic lower extremity amputations. Incidence, risk factors, and prevention- a 12 year follow-up study in Nauru. Diabetes Care 19:710–714, 1996.
48. International Working Group on the Diabetic Foot. International Consensus on the Diabetic Foot, Amsterdam, The Netherlands, 1999
49. Ishii Y, Miyanaga Y, Shimojo H, Ushida T, Tateishi T. Effects of hyperbaric oxygen on procollagen messenger RNA levels and collagen synthesis in the healing of rat tendon laceration. Tissue Eng 1999;5: 279-86.
50. Keenan, A.M., Tindel, N.L., Alavi, A. Diagnosis of pedal osteomyelitis in diabetic patients using current scintigraphic techniques. Arch. Intern. Med. 149:2262–2266, 1989.
51. Kindwall EP. The physics of diving and hyperbaric pressures. In: Kindwall EP, Whelan HT, ads. Hyperbaric Medicine Practice. Flagstaff, Ariz: Best Publishing Co; 1999:21-36.
52. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. Arch Surg 1984;119:199-204.
53. Laing, P. Diabetic foot ulcers. Am. J. Surg. 167(Suppl. 1A):31S–36S, 1994.
54. Laing, P.W., Cogley, D.I., Klenerman, L. Neuropathic foot ulceration treated by total contact casts. J. Bone Joint Surg. 74-B:133, 1992.
55. Larsson, J., Agardh, C.-D., Apelqvist, J., Stenstrom, A. Long term prognosis after healed amputation in patients with diabetes. Clin. Orthop. 350:149–158, 1998.
56. Lavery, L.A., Armstrong, D.G., Vela, S., Quebedeux, T.L., Fleischli, J.G. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch. Intern. Med. 158:157–162, 1998.
57. Lavery, L.A., Ashry, H.R., van Houtum, W., Pugh, J.A., Harkless, L.B., Basu, S. Variation in the incidence and proportion of diabetes-related amputations in minorities. Diabetes Care 19:48–52, 1996.
58. Lazarus, G.S., Cooper, D.M., Knighton, D.R., Margolis, D.J., Pecoraro, R.E., Rodeheaver, G., Robson, M.C. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch. Dermatol. 130:489–493, 1994.
59. Lee, J.S., Lu, M., Lee, V.S., Russel, D., Bahr, C., Lee, E.T. Lower-extremity amputation. Incidence, risk factors, and mortality in the Oklahoma Indian Diabetes Study. Diabetes 42:876–882, 1993.
60. Lehto, S., Ronnemaa, T., Pyorala, K., Laakso, M. Risk factors predicting lower extremity amputations in patients with NIDDM. Diabetes Care 19:607–612, 1996.
61. Leichter, S.B., Allweiss, P., Harley, J.,Clay, J., Kuperstein-Chase, J., Sweeney, G.J., Kolkin, J. Clinical characteristics of diabetic patients with serious pedal infections. Metabolism 37:22, 1988.
62. Levin, M. Diabetic foot wounds. pathogenesis and management. Adv. Wound. Care 10:24–30, 1997.
63. Lew, D.P., Waldvogel, F.A. Osteomyelitis. N. Engl. J. Med. 336:999–1007, 1997
64. Lipsky, B.A. Osteomyelitis of the foot in diabetic patients. Clin. Infect. Dis. 25:1318–1326, 1997.
65. Lipsky, B.A., Pecoraro, R.E., Wheat, L.J. The diabetic foot: soft tissue and bone infection. Infect. Dis. Clin. North Am. 4:409–432, 1990.
66. LoGerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N Engl J Med 1984;311:1615-9.

67. LoGerfo FW, Misare FD. Current management of the diabetic foot. Adv Surg 1997;30:417-26.
68. LoGerfo FW. Vascular disease, matrix abnormalities and neuropathy: implications for limb salvage in diabetes mellitus. Journal of Vascular Surgery 1987;5:793-796.
69. Longmaid, H.E., Kruskal, J.B. Imaging infections in diabetic patients. Infect. Dis. Clin. North Am. 9:163–182, 1995
70. Mayfield, J.A., Reiber, G.E., Sanders, L.J., Janisse, D., Pogach, L.M. Preventive foot care in people with diabetes: technical review. Diabetes Care 21:2161–2177, 1998.
71. McNeely, M.J., Boyko, E., Ahroni, J.H. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration: How great are the risks? Diabetes Care 18:216–219, 1995.
72. Ministry of Health. Clinical Practice Guidelines – Diabetes Mellitus, 1999
73. Moss, S., Klein, R., Klein, B. The 14-year incidence of lower extremity amputations in a diabetic population: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 22:951–959, 1999.
74. Mueller Mi, Diamond JE, Elitto A, Sinacore DR. Insensitivity, limited joint mobility and plantar ulcers in patients with diabetes mellitus. Physical Therapy 1 989;69:453-459.
75. Mueller, M.J., Diamond, J.E., Sinacore, D.R., Delito, A., Blair, V.P., Drury, D.A., Rose, S.J. Total contact casting in treatment of diabetic plantar ulcers; controlled clinical trial. Diabetes Care 12:384–388, 1989.
76. Nelson, R.G., Gohdes, D.M., Everhart, J.E., Hartner, J.A., Zwemer, F.L., Pettit, D.J., Knowler, W.C. Lower extremity amputations in NIDDM: 12-yr follow-up study in Pima Indians. Diabetes Care 11:8–16, 1988.
77. Palumbo, P.J., Melton, L.J. Peripheral vascular disease and diabetes. In: Diabetes in America. Data Complied 1984 (NIH publ. no. 85-1486), p. l. US Government Printing Office. Washington D.C, 1985
78. Pecoraro, R.E., Reiber, G., Burgess, E.M. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care 13:513, 1990.
79. Plafki C, Peters P, Almeling M, Welslau W, Busch R. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 2000;71:119-24.
80. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med 1982;72:439-50.
81. Reiber, G.E., Boyko, E.J., Smith, D.G. Lower extremity foot ulcers and amputations in diabetes. In: Diabetes in America, 2nd ed. (NIH publ. no 95-1468) edited by M.I. Harris, C. Cowie, and M.P. Stern, US Government Printing Office, Washington D.C, 1995
82. Reiber, G.E., Pecoraro, R.E., Koepsell, T.D. Risk factors for amputation in patients with diabetes mellitus: a case-control study. Ann. Intern. .Med. 117:97–105, 1992.
83. Reiber, G.E., Vileikyte, L., Boyko, E.J., Del Aguila, M., Smith, D.G., Lavery, L.A., Boulton, A.J.M. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care 22:157–162, 1999.
84. Resnick, H.E., Valsania, P., Phillips, C.L. Diabetes mellitus and nontraumatic lower extremity amputation in Black and White Americans. Arch. Intern. Med. 159:2470–2475, 1999.
85. Ritz, G., Kushner, D., Friedman, S. A successful technique for the treatment of diabetic neurotrophic ulcers. J. Am. Podiatr. Med. Assoc. 82:479–481, 1992.
86. Shaw, J.E., Boulton, A.J.M. The pathogenesis of diabetic foot problems. An overview. Diabetes 46 (suppl.):S58–S61, 1997.
87. Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. Arch Surg 2000;135:1293-7.
88. Selby, J.V., Zhang, D. Risk factors for lower extremity amputation in persons with diabetes. Diabetes Care 18:509–516, 1995.
89. Sosenko JM, Kato M, Soto R, Bild DE. Comparison of quantitative sensory threshold measures for their association with foot ulceration in diabetic patients. Diabetes Care 1990;13:10571061
90. Steed, D.L., Donohoe, D., Webster, M.W., Lindsley, L., Diabetic Ulcer Study Group. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. J. Am. Coll. Surg. 183:61–64, 1996.
91. Steed, D.L., Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. J. Vasc. Surg. 21:71–81, 1995.
92. Strandness DEJ, Priest RE, Gibbons GE. Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. Diabetes 1964;13:366-72.
93. Tentolouris, N., Jude, E.B., Smirnofl, Knowles, E.A., Boulton, A.J.M. Methicillin-resistant Staphylococcus aureus. an increasing problem in a diabetic foot clinic. Diabetic Med. 16:767–771, 1999.
94. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med 1996;334:1642-8.
95. Tompach PC, Lew D, Stoll JL. Cell response to hyperbaric oxygen treatment. Int J Oral Maxillofac Surg 1997;26:826.
96. Wagner FW Jr. The diabetic foot. Orthopaedics 1987; 10:163-72
97. Watkins PJ, Edmonds ME. Sympathetic nerve failure in diabetes. Diabetologia 1983;25:73-77.
98. Young, M.J., Breddy, J.L., Veves, A., Boulton, A.J.M. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. Diabetes Care 17:557–560, 1994.