Management of the diabetic foot

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Over the past few decades, diabetes mellitus (DM) has emerged as one of the most prevalent chronic diseases worldwide. In Malaysia, a recent study reported that the overall prevalence of DM among Malaysians was 22.9% in 2013, and 12.1% of them were newly diagnosed diabetics. Diabetic foot is one of the major concerns of the complications of chronic diabetes and is defined as a foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. The incidence of diabetic complications result in increased hospital bed occupancy and account for the increasing healthcare cost and resource use. Diabetic foot gangrene and amputation are significant complications of the disease. In 1998, foot complications contributed to 12% of all diabetic admissions and 17% of all hospital admissions in Hospital Kuala Lumpur, Malaysia. Diabetic foot complications arise from a complex interplay of ulceration and infection. Diabetic foot ulceration can affect people with both type 1 and type 2 diabetes. Foot ulcer refers to a patch of broken down skin, usually at feet or on the lower part of the leg. People with diabetes are most likely to get a foot ulcer when glucose levels are high, which may lead to poor skin healing due to damage of nerves that carry pain sensation from the feet to the brain. The risk of developing a foot ulcer is increased up to seven-fold in diabetic patients with neuropathy as compared to non-neuropathic diabetic patients. DM also affects the autonomic nervous system, leading to dryness and fissuring of the skin, making it prone to infection. Diabetic foot infection (DFI) is usually precipitated by trauma and arises either as skin ulceration secondary to peripheral neuropathy or as a wound. Various microbiorganisms may colonize the wound and cause further tissue damage. This may then be followed by a host response accompanied by inflammation and infection. Infections may start superficially in an ulcer or crack of the skin and then spread contiguous and can affect deeper tissues, often resulting in bone death. Prevalence 

Diabetic foot ulcer (DFU) affects 15% of people with diabetes. The rate of diabetic foot increases by year. In the National Health and Morbidity Survey 2006 conducted by the Health Ministry, 4.7% of known diabetics had undergone toe or leg amputations. A study in Penang showed about 1% of known diabetics presented with self-medicated ulcers or had undergone amputations. The prevalence of foot ulceration in patients attending a diabetic clinic in Malaysia was reported as high as 6%. In the US, the American Diabetes Association (ADA) has reported that up to 25% of people with diabetes will experience a foot ulcer at some point in their lifetime. The ADA also states that 14-24% of people with a foot ulcer will die from their disease. Approximately 15-20% of people with diabetes in the US will be hospitalized with a foot complication at some point during the course of their disease. In the US, people with diabetes are 25 times more likely to lose a leg than people without the condition. The Thomson Reuters ISI Web of Science for 2010 reported a steadily increasing number of published reports on DFU; the yearly number of published items rose from less than 20 in the 1990s to about 100 in the past few years. According to Dr PC Chye, a consultant orthopedic surgeon of Hospital Kuala Lumpur, Malaysia, 15-25% of diabetics will develop a foot ulcer and from this figure, 40-80% will be infected. Forty-nine percent of diabetic patients with DFU will develop infection in the other foot in another 18 months.

Risk factors 

The risk of foot ulceration and limb amputation were found to be associated with age, gender, geographical location and socio-economic status. Diabetic foot problems are common in patients <40 years of age. The incidence increases with age >40 years and occur most commonly in those aged 50 years and older. However, duration and control of diabetes are greater predictors of diabetic foot problems than chronological age. Male patients with diabetes are at increased risk of foot ulcers or amputation compared with women. In developed countries, people with diabetes will have a foot ulcer during their lifetime and the incidence is even more common in developing countries. Diabetest patients in lower socioeconomic groups are at high risk of developing diabetic foot disorders since they have limited access and resources for diabetes complication prevention programs and also proper footwear. Peripheral neuropathy, vascular disease, and infection are the major factors found to cause diabetic foot ulcer. The presence of trauma and foot deformity with these factors would exaggerate lower limb amputation. Diabetic neuropathy, peripheral arterial disease and infection is an important risk factors of development of diabetic foot ulcer. Among the three factors, diabetic neuropathy was identified as the most common factor, almost 90% of diabetic foot ulcer cases. Structural deformities and abnormalities such as flatfoot, pes cavus, Charcot foot, and Charcot neuropathy and hammer foot play an important role in the pathway of diabetic feet since they contribute to abnormal plantar pressures and therefore provide a microenvironment to ulceration. The common general, systemic and local risk factors are shown in Figure 1. Local risk factors are frequently related to peripheral neuropathy as it is the primary leading cause of diabetic foot ulcerations. About 45-60% of diabetic ulceration cases have purely neuropathic causes, while up to 45% have neuropathic and ischemic components. Trauma to the foot, in the presence of sensory neuropathy and improperly fitted shoes, is also a major risk factor of ulceration, as it will lead to callus formation. Other factors that may contribute to risk of ulceration include duration of diabetes, poor diabetes control, chronic renal disease and viral or fungal infections. Treatment of ulceration 

Diabetic foot ulceration is a major diabetes complication and its management requires a multidisciplinary approach. Proper treatment for diabetic foot ulcer can lower the risk of limb amputations. Physical examination of the diabetic foot is based on the assessment of the skin and the vascular, neurological, and musculoskeletal systems. The dermatological examination includes a visual inspection of the skin of the legs and feet, particularly the dorsal, plantar, medial, lateral and posterior aspects. The dermatological examination of each toe is also done. Debridement of the wound, management of infections and off-loading of the ulcer are the most common treatment employed for diabetic foot ulcer. Hyperbaric oxygen therapy, use of advanced wound care products and growth factors are also beneficial as addition therapies. Debridement is the removal of all non-viable tissues and slough from the ulcer. It is usually performed classically under surgical, mechanical, enzymatic, biological and autolytic methods. Debridement of necrotic tissues would only be carried out after thorough debridement and application of topical wound healing agents, dressings or wound closure procedures. It improves healing by promoting the production of granulation tissue. Surgical debridement, also known as the 'sharp method,' is an important tool for use in the management of diabetic foot ulcers. Surgical debridement involves removal of all nonviable tissue/bone until healthy, bleeding ulcer bed is encountered. Diabetic foot ulcers may require immediate incision and drainage. Osteomyelitic bones, bone fragments, and foreign body digits require resection or partial amputation. This procedure is performed using scalpels and is rapid and effective in removing hyperkeratosis and dead tissue. Using a scalpel blade with the tip pointed at a 45° angle, all nonviable tissue must be removed until a healthy healing ulcer bed is produced with cautery of the wound edges. Mechanical debridement is a non-selective method that physically removes debris from the wound. Examples of mechanical debridement include wet-to-dry dressings, high-pressure irrigation and whirlpool therapy. Wet-to-dry dressings cause mechanical separation of eschar from the wound bed once the dressing is removed. High-pressure irrigation involves the use of a pressurized stream of water. It removes bacteria and necrotic debris from wounds but could drive bacteria into soft tissue. whirlpool therapy is another form of powered irrigation which loosens and removes necrotic tissue, debris and wound exudate. This is suitable for non-pressurized wounds but not for those with fragile granulation tissue. Enzymatic debridement uses topical proteolytic enzymes as an adjunct in managing chronic wounds. It uses a variety of enzymatic agents, including collagenase, papain, and a combination of streptokinase and streptodornase. These are also used in the treatment of non-healing diabetic wounds. Autolytic debridement is also effective in the elimination of drug-resistant pathogens, such as methicillin-resistant Staphylococcus aureus, from wound surfaces. Autolytic debridement occurs naturally in healthy, moist wound environment with adequate circulation. It involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body’s enzymes. Analysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels and films. It is highly selective, avoiding damage to the surrounding skin. Hyperbaric oxygen therapy is another powerful and potentially beneficial debridement method. The ‘sharp method,’ significantly contributes to the healing process of the wound, including the diabetic ulcer.

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Off-loading 

Off-loading is a treatment to reduce the pressure to the DFU and hence reducing the trauma to the ulcer and allowing it to heal. Off-loading of the ulcer area is extremely important for the healing of plantar ulcers. Numerous studies have shown that elevated plantar pressures significantly contribute to the development of plantar ulcers in diabetic patients. Furthermore, any existing foot deformities may increase the risk of ulceration, especially in the presence of diabetic peripheral neuropathy and inadequate off-loading. Inadequate off-loading of the ulcer also contributed significantly to the delay of ulcer healing. Off-loading reduces high-pressure irrigation involves the use of a pressurized stream of water. It removes bacteria and necrotic debris from wounds but could drive bacteria into soft tissue. Whirlpool therapy is another form of powered irrigation which loosens and removes necrotic tissue, debris and wound exudate. This is suitable for non-pressurized wounds but not for those with fragile granulation tissue. Enzymatic debridement uses topical proteolytic enzymes as an adjunct in managing chronic wounds. It uses a variety of enzymatic agents, including collagenase, papain, and a combination of streptokinase and streptodornase. These are also used in the treatment of non-healing wounds but not for those with fragile granulation tissue. Autolytic debridement is also effective in the elimination of drug-resistant pathogens, such as methicillin-resistant Staphylococcus aureus, from wound surfaces. Autolytic debridement occurs naturally in healthy, moist wound environment with adequate circulation. It involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body’s enzymes. Analysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels and films. It is highly selective, avoiding damage to the surrounding skin. Hyperbaric oxygen therapy is another powerful and potentially beneficial debridement method. The ‘sharp method,’ significantly contributes to the healing process of the wound, including the diabetic ulcer.

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The most effective method of off-loading is the non-removable total-contact cast (TCC). It is made of low costs materials of plaster or foam or soft plastic and is non-removable. Non-removable TCCs are indicated for effective off-loading of ulcers located at the forefoot or midfoot. Severe foot ischemia, critical limb ischemia, and/or skin and/or poor skin quality are absolute contraindications to the use of a non-removable TCC. Non-removable TCCs are effective in off-loading the plantar pressures from the forefoot and midfoot to the heel. They allow complete rest of the foot whilst also permitting restricted activity. Non-removable TCCs have been applied recently using sterile maggots. Maggots have the ability to digest surface debris, bacteria and necrotic tissue, leaving healthy tissue intact. Recent reports suggest that this method is also effective in the elimination of drug-resistant pathogens, such as methicillin-resistant Staphylococcus aureus, from wound surfaces.

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also reduce edema and compliance with treatment is high. Other topical agents that have shown some potential benefits in clinical trials are:

(i) Growth factors, (becaplermin gel, autologous platelets) for use in neuropathic diabetic ulcers but contraindicated in infected and necrotic wounds. However, these preparations are currently unavailable in Malaysia.

(ii) Hyperbaric oxygen therapy is available in certain centers in Malaysia and is used as an adjunctive treatment for hypoxic diabetic foot ulcers. It is applied in the form of a once-daily gel along with debridement on a weekly basis. Initial studies have indicated a significant positive effect of becaplermin on ulcer healing; however, more recent studies have reported an increased risk of infection in patients treated with becaplermin, especially at high doses. Consequently, the US FDA has published a warning of an increased risk of cancer if more than three treatments of becaplermin are used. Further studies are necessary to explore the benefit-to-risk ratio and the cost effectiveness of this therapy.

Platelet-rich plasma (PRP)
PRP is an autologous product, extracted from the patient’s plasma, which includes a high platelet concentration in a fibrin clot which is applied to the ulcer area. The fibrin clot is absorbed during wound healing within days to weeks following its application. There are limited studies reporting a shorter closure time and higher healing percentage in patients using PRP and platelet-derived products. However, further studies are required in order to support the possible beneficial effect of this method in ulcer healing.

Hyperbaric oxygen
Limited numbers of randomized controlled trials are available to support the use of hyperbaric oxygen for ulcer healing. Treatment with hyperbaric oxygen therapy involves the intermittent administration of 100% oxygen at a pressure greater than that at sea level. The risk of this method is that fibroblasts, endothelial cells and keratinocytes are replicated at higher rates in an oxygen-rich environment. In addition, leukocytes kill bacteria more effectively when supplied by oxygen. According to current guidelines, hyperbaric oxygen can be applied as an adjunctive therapy for patients with severe soft-tissue foot infections and osteomyelitis who have not responded to conventional treatment.

Treatment for DFI
DFI is usually secondary to ulceration. Treatment requires early incision and drainage or debridement and empirical broad-spectrum antibiotic therapy. If there is co-existing gangrene or extensive tissue loss, early amputation at the appropriate level should be considered to remove the risks of infection. The essential components of the treatment of diabetic foot infections are surgical treatment, antibiotic treatment, wound care, treatment of metabolic and co-morbidities, frequent assessment of treatment response, patient education, prevention and orthotics or prosthesis management.

Platelet-derived growth factor (PDGF-beta) (becaplermin) is a topical therapy for the treatment of non-infected diabetic foot ulcers. It is applied in the form of a once-daily gel along with debridement and daily gel along with debridement, using PRP and platelet-derived growth factors. The fibrin clot is absorbed during wound healing within days to weeks following its administration. Initial treatment is then re-evaluated before any further action could be taken.

Limb-threatening infection
Patients with limb-threatening infections are managed as outpatients and hospitalized when no improvement is noted after 48-72 hours or as the condition deteriorates. Initial treatment in a previously untreated patient with a non-limb-threatening infection is focused on Staphylococcus and Streptococcus sp. Antibiotic therapy is commenced if ulcer is present. The ulcer is cleansed and debrided. Ulcer management is then followed as previously outlined. Correction of hyperglycemia and stabilization of other co-morbidities are carried out simultaneously. The response to treatment is then re-evaluated after 48-72 hours before any further action could be taken.

Limb-sparing treatment
Patients with limb-sparing infections should be hospitalized for appropriate management. The management steps include surgical treatment, wound care, antibiotic treatment, control of hyperglycemia, assessment of treatment response and treatment follow-up. Initial treatment of limb-sparing infections requires broad-spectrum antibiotic coverage (Staphylococcus aureus, group B streptococcus, enterobacteriaceae and anaerobes). Surgical treatment is necessary to be done early. Surgery on the infected site includes debridement of wounds, incision and drainage of abscesses, necrotizing fasciitis and amputations of gangrenous tissues. Tissues taken deep from the wound are sent for aerobic and anaerobic cultures. Whenever possible, osteomyelitis bones are removed and sent for microbiological culture and histology. Wound care includes cleansing, debridement, packing and dressing of wound. Wound management is then followed as described under the section of DFUs. All clinically infected diabetic foot wounds require antibiotic therapy. A successfully treated DFI requires appropriate wound care. The initial step for antibiotic treatment is selection of empirical antibiotic regimen and assessment of infection severity, while awaiting culture and sensitivity test (C&S) results. The empirical therapy should be based on severity of infection and available microbiological data, such as recent C&S results and the local prevalence of pathogens, especially pattern on antibiotic resistant strains. Factors such as costs, patient tolerance, allergies, potential relapse or liver adverse effects, ease of administration and local antibiotic resistance patterns should be considered when designing regimens for patients. For mild and moderate non-limb-threatening infections, usually monomicrobial, with Staphylococcus aureus, Staphylococcus epidermidis and Streptococci being the most common infecting organisms, it may be prudent to treat mild infections in immuno-compromised patients with broad-spectrum antibiotics. The treatment duration with antibiotics should be based on the severity of infection. It takes around 1-2 weeks for mild-to-moderate infections and more than 2 weeks for more serious infections. However, for osteomyelitis, if infected bone is not removed, antibiotics are given for 6-8 weeks, depending on C&S results. If all infected bone is removed, a shorter course (1-2 weeks) of antibiotics, as for soft tissue infection, may be adequate.

Control of hyperglycemia, electrolyte imbalance and stabilization of other co-morbidities are then carried out simultaneously. Reassessment of treatment response should take place regularly. If infection has subsided but ulcer persists, then principles of DFU treatment should be followed. Once infection and ulcer has healed, the residual foot needs close follow up. Aspects of prevention, patient education, podiatric care and off-loading measures should then be undertaken.

Role of pharmacists
Prevention is the best way of dealing with DFUs. Pharmacists based in the hospital or community play an essential role in prevention and management of diabetic foot. Pharmacists may advise patients on proper foot care by paying a serious attention to cuts, abrasions and blisters as this would limit severe wounds from forming. The principle of treatment is that the healed ulcers must be prevented from recurring. This will require a multidisciplinary approach with committed, dedicated professionals including the podiatrist, orthopaedic surgeon, vascular surgeon, endocrinologist, physician, infection control nurse, cardiologist, nephrologist and neurologist. Preventive measures include proper and regular podiatric management of calluses, proper footwear, foot hygiene, ingrown toe nails and therapeutic footwear with high toe box.

Pharmacists should frequently remind their diabetic patients to wear socks and properly fitting closed-toe footwear, to moisturize and visually inspect their feet nightly, and to see doctors for evaluation of cracks, sores, and other injuries. Pharmacists should empower patients with diabetes to achieve optimal blood glucose and blood pressure control through individualized diet and exercise and medication adherence, since worsening control contributes to the development of neuropathy, peripheral vascular disease and infections.

Once a foot infection develops, the pharmacist should engage with other healthcare professionals to select the most appropriate antimicrobial regimen for the patient, including dosage, route of administration, frequency and duration of therapy. The pharmacist should apply their pharmacological knowledge by assisting in monitoring the efficacy and safety of the patient’s prescribed antibiotic regimen. Regular foot examination, patient education, simple hygiene practices, provision of appropriate footwear, and prompt treatment of minor injuries can decrease ulcer occurrence by 50% and eliminate the need for major amputation in nonischemic limbs.

In conclusion, pharmacists play an essential role in preventing DFU and DF and therefore reduce the risk of lower limb amputation by providing pharmaceutical care and thus, enhance patients’ quality of life.


