Comprehensive Review on Diabetic Foot Ulcer – A Brief Guide to Pharmacists

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Abstract: Diabetic foot ulcers are common among diabetes patients, have a long term impact on the morbidity, mortality and quality of patients lives. The pathogenesis of foot ulcer is multi factorial and management requires early assessment in a multidisciplinary set up. Interventions should be directed at infection, peripheral ischemia, and abnormal pressure loading caused by peripheral neuropathy and limited joint mobility. Without early and optimal intervention, the wound can rapidly deteriorate leading to amputation of the affected limb. Multidisciplinary management programs that focus on prevention, education, regular foot examinations, aggressive intervention, and optimal use of therapeutic footwear have demonstrated significant reductions in the Incidence of lower extremity amputations. Pharmacists play a key role in education, medication, monitoring, and motivational support for people with diabetes and its complications. This article provides a comprehensive review of the epidemiology, pathophysiology, treatment modalities and information on prevention of diabetic foot ulcers for Community, Hospital, Clinical and Student Pharmacists. Enhancing pharmacist’s knowledge can influence in positive health outcomes as there are strong evidence that patient counseling can improve patient compliance and quality of life in diabetes population. Pharmacists can utilize their clinical expertise in monitoring and managing diabetic foot ulcer plans to empower patients to actively manage their health. Pharmacists can serve as a resource to other health care providers to implement an assured safe, appropriate, cost-effective diabetic foot ulcer management.

Key words: Diabetes, diabetic foot ulcer, wounds, antimicrobials, amputation, clinical pharmacy intervention.

Introduction:

Diabetic foot syndrome is defined as ulceration or destruction of lower limb tissues in diabetic patients associated with neuropathy, with a different stage of ischemic disease of the lower limbs; often with infection [1]. Patients with diabetes have a 15–25% lifetime risk of developing a foot ulcer and a 50% to 70% recurrence rate over the ensuing 5 years. Foot Complications are a major cause of morbidity and mortality in persons with diabetes and contribute to increased healthcare utilization and costs. Only two thirds of these ulcers are expected to heal. The median time taken for healing of these ulcers is approximately 6 months, up to 28% may result in some form of amputation survival of amputee patient’s life expectancy was 4.32 years in a study [2,3]. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low and middle-income countries than in high-income countries. Early detection and effective management can reduce the severity of complications, including preventable amputations [4]. This article provides a comprehensive review of the current state of the problem, epidemiology, pathophysiology, treatment modalities.
and prevention of diabetic foot ulcers for Pharmacists. Pharmacists can utilize their knowledge and clinical expertise in monitoring and managing diabetic foot ulcer plans to empower patients to actively manage their health.

The Burden of Diabetes Mellitus and its Complications

Type2 diabetes constitutes about 85 to 95% of all diabetes in high-income countries and accounts for an even higher percentage in low- and middle-income countries. Type 2 diabetes is now a common and serious global health problem, which, for most countries, has evolved in association with rapid cultural and social changes, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns. The incidence and prevalence of type 2 diabetes is also reported to be increasing in children. Studies from America and Japan have demonstrated an increasing incidence.[5]

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges. Foot problems account for more hospital admissions than any other long-term complications of diabetes and also result in increasing morbidity and mortality.[6]. Around 90,000 amputations are done yearly as a result of non-traumatic diabetic foot complications. A study reported that people of elder group are at a greater risk of developing foot ulcers and more susceptible to abscess and osteomyelitis. And hence people of these countries will be disposed to ulceration. Diabetic foot patients may further develop more complications and therefore proper management is required in a multidisciplinary approach.[7].

Etiology

The development pathway towards ulceration is multi-factorial. The etiologies of diabetic ulceration include neuropathy, arterial disease, pressure and foot deformity. Diabetic peripheral neuropathy, present in 60% of diabetic persons and 80% of diabetic persons with foot ulcers, confers the greatest risk of foot ulceration; micro-vascular disease and sub-optimal glycemic control contribute.

Risk Factor

Risk factors for foot ulcer include male gender, duration of diabetes more than 10 years, peripheral neuropathy, foot deformity, peripheral vascular disease, smoking, hypertension, history of prior ulcers or amputation, poor glycemic control, genetic[8] and nutritional factors, diabetic retinopathy and nephropathy and anatomical deformities, environmental factors peripheral vascular disease.

Pathophysiology

Diabetic foot ulcers are chronic wounds that fail to heal in a regulated and systematic manner due to multiple abnormal physiologic, anatomic, and cellular factors. The decreased angiogenic response and ischemia endothelial dysfunction and increased susceptibility to wound infection. In addition, in the Diabetic foot ulcers there is poor and disorganized regulation of the cytokines, growth factors, proteases, extracellular matrix components, and cells needed to achieve complete wound closure. The keratinocyte migration and proliferation is impaired and fibroblast response to growth factors and the ability to synthesize collagen is impaired.

There is a relative deficiency of tissue inhibitors of matrix metalloproteinases, which results in degradation of the extracellular matrix.[9]. All these pathophysiologic factors contribute to the poor healing rates observed in patients with Diabetic foot ulcers.
Classification of diabetic foot ulcers

Several schemes have been used to classify diabetic foot ulcers, but none of them has been accepted universally. The following are the most commonly used classifications.\[10\]

Wagner-Meggitt Classification

Wagner-Meggitt, the most popular method, has been used for decades to classify DFUs in six grades based on the wound’s depths and extent of gangrene.

Table: 1 Wagner Classification of Diabetic Foot Ulcer

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No ulcer in a high risk foot</td>
</tr>
<tr>
<td>1</td>
<td>Superficial ulcer involving the full skin thickness but not underlying tissues.</td>
</tr>
<tr>
<td>2</td>
<td>Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.</td>
</tr>
<tr>
<td>3</td>
<td>Deep ulcer with cellulitis or abscess formation, often with osteomyelitis.</td>
</tr>
<tr>
<td>4</td>
<td>Localized gangrene.</td>
</tr>
<tr>
<td>5</td>
<td>Extensive gangrene involving the whole foot.</td>
</tr>
</tbody>
</table>
The University of Texas Wound Classification

The University of Texas classification is a more comprehensive scale and includes risk stratification and expresses tissue breakdown, infection and gangrene separately. Although Texas classification describes the grade of wound in more details, it does not include measures of neuropathy or ulcer area\(^\text{[11]}\).

Table 2: The University of Texas Wound Classification System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>pre- or post ulcerative completely epithelized lesion</td>
<td>Superficial wound</td>
<td>Wound penetration up to tendon or capsule</td>
<td>Wound penetration up to bone or joint</td>
</tr>
<tr>
<td>B</td>
<td>Infection</td>
<td>Infection</td>
<td>Infection</td>
<td>Infection</td>
</tr>
<tr>
<td>C</td>
<td>Ischemia</td>
<td>Ischemia</td>
<td>Ischemia</td>
<td>Ischemia</td>
</tr>
<tr>
<td>D</td>
<td>Infection and ischemia</td>
<td>Infection and ischemia</td>
<td>Infection and ischemia</td>
<td>Infection and ischemia</td>
</tr>
</tbody>
</table>

PEDIS (Perfusion, extent, depth, Infection, and sensation)

Another validated classification system for DFUs that includes the severity of infection is the PEDIS (perfusion, extent, depth, infection, and sensation) system. PEDIS classification was proposed by the International Working Group on the Diabetic Foot and grades the wounds on the basis of five features: perfusions (arterial supply), extent(area), depth, infection and sensation. There are levels of 1 to 4 for each of these factors. The in-depth nature of this system is appropriate for the research community that desires this amount of detail.

Table 3: The International Working Group on the Diabetic Foot risk categorization tool

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sensory neuropathy</td>
</tr>
<tr>
<td>1</td>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>2</td>
<td>Sensory neuropathy and foot deformity</td>
</tr>
<tr>
<td>3</td>
<td>Previous ulcer or amputation</td>
</tr>
</tbody>
</table>

Treatment

General Management

Management of DFUs is complex and requires a systematic approach to achieve more consistent and successful outcome. This includes addressing multiple issues like treat peripheral artery disease, neuropathy, nutritional status, ulcer and bone infection and glycemic control is needed.

Infection Control

Fungal infections are also common in diabetic foot patients. However it is not uncommon to have a predominance of mono-microbial infection in diabetic foot.

The Predominant pathogens causing diabetic foot infections are gram-positive cocci, however other pathogens are involved so infection\(^\text{[12,13]}\) should be considered polymicrobial. Appropriate wound swab cultures or bone biopsy cultures should be required for proper management of infection. For mild, soft tissue infection, oral antibiotics are good enough. Moderate to severe infections require parenteral, combination therapy. The use of topical antibiotics is usually not recommended. The prevention of infection is not achieved through the use of medications but could be achieved with patient education; foot hygiene, proper protection of pressure points and early local care of shallow ulcers.
### Infection Severity

<table>
<thead>
<tr>
<th>Mild (usually treated with oral agent(s))</th>
<th>Probable Pathogen(s)</th>
<th>Antibiotic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus (MSSA); Streptococcus spp</td>
<td>Dicloxacillin; clindamycin; Cephalexin; Levofloxacin; Amoxicillin-clavulanate</td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus (MRSA)</td>
<td>Doxycycline; Trimethoprim/sulfamethoxazole</td>
<td></td>
</tr>
</tbody>
</table>

| Moderate [may be treated with oral or initial parenteral agent(s)] | MSSA; Streptococcus spp; Enterobacteriaceae; Obligate anaerobes | Levofoxacin; Cefoxitin; Ceftriaxone; Ampicillin-sulbactam; Moxifloxacin; Ertapenem; Tigecycline; Levofloxacin; Ciprofloxacin; Clindamycin; Imipenem-cilastatin |

| MRSA | Linezolid; Daptomycin; Vancomycin |
| Pseudomonas aeruginosa | Piperacillin-tazobactam |
| MRSA, Enterobacteriaceae, Pseudomonas and Obligate anaerobes | Vancomycin plus one of the following: Ceftazidime; Cefepime; Piperacillin-tazobactam; Aztreonam; or a carbapenem |

### Ulcer Care

Daily or more frequent cleaning and dressing are essential requirements. Regular daily bathing in saline or dilute antiseptic solution offers a better chance of cleaning the ulcers, compared with dressing alone. Most chronic foot ulcers occur among elderly diabetics. However, when chronic ulcers occur in healthy younger patients, surgical closure with special techniques could be considered.

### Ulcer Surgery

Chronic ulcers are the result of prolonged biological hazards. Therefore, good outcomes are measured in weeks and months rather than days. At least six to ten weeks is the expected time for healing of these complicated lesions. Breakdown of split-skin-grafted areas is common with daily ambulation and footwear pressure.

### Surgery to Facilitate Ulcer Healing

Chronic diabetic foot ulcers combined with functional problems add further risks to the formation of more ulcers. Such situations can arise when the Achilles tendon becomes tight as a result of prolonged disuse of the ankle. The plantar flexed ankle imposes more pressure on the metatarsal heads which may be responsible for pressure ulcer development. The tight Achilles tendon can be lengthened, so as to release metatarsal head pressure. After the lengthening, there is an initial weakening of the plantar flexion pull which returns to normal in approximately eight months time. At the same time as releasing of the metatarsal head pressure, the metatarsal head can be removed, via the plantar ulcer or via separate incisions. The diabetic patient with chronic ulceration of the foot often has co-existing deformities which might need to be corrected to prevent ulcer recurrence or new ulcer development. Surgery may involve joint fusion at the site of the arthropathy or in the most unstable late cases, amputation.
Supportive Treatment

Abnormal pressure points undoubtedly predispose the diabetic foot to ulceration. Protecting the pressure points, therefore, becomes vital for the prevention of ulcer formation. However, most diabetic ulcers are complicated by peripheral arterial disease and infection. Therefore, pressure relieving devices are important mostly after treatment interventions and ulcer healing.

Oxygen therapy

Oxygen therapy, for the majority of people, is also known as hyperbaric oxygen treatment. The pressure around the limb is kept just above atmospheric pressure. Topical oxygen will diffuse into the ulcer area to enhance healing.

Toe Amputations

Digital amputations are the most common amputations performed in the foot. Amputation of the great toe greatly reduces the thrust force during the gait, where the hallux with the flexor hallucis longus and flexor brevis play a fundamental role, with possible metatarsalgia of the 2nd and 3rd rays. The amputation of a central toe (2nd, 3rd or 4th) causes foot instability, not only because of the digitigrades contribution during the gait, but especially because it can cause deformities of the adjacent toes.

Ray Amputations

Amputation of the first ray causes, in addition to a deficiency in the boost phase of the step and the loss of plantar-flexion of the toe, a collapse of the medial column with a possible evolution towards a pronated and valgus foot. It may also lead to ulcerative lesions or stress fractures of the other rays. It is important to keep the insertion of the anterior tibial tendon and peroneus longus tendon on the metatarsus, leaving a functionally valid foot, if necessary with the use of an orthotic prosthesis.

The amputation of a central ray is functionally more effective because it only slightly reduces the latero-medial diameter of the forefoot, without biomechanical deficits. The amputation of the fifth ray can cause a varus, adducted and supinated foot, because of the prevalence of the posterior tibial tendon, with possible ulcerative lesions or stress fractures.

Transmetatarsal Amputation

Transmetatarsal amputation (TMA) is typically performed in patients with chronic osteomyelitis involving the forefoot, gangrene of the toes, or a non-healing ulceration with a previously resected first-ray. As mentioned earlier, a first-ray resection alters normal gait characteristics and patients are at higher risk for developing transfer lesions, putting them at risk for subsequent amputation. The resection of multiple central rays results in a non-functional foot and a TMA is indicated to prevent multiple amputations.

The amputation must be made at the bases of all the five metatarsals, leaving intact the areas of attachments of tibialis anterior and peroneus brevis on the first and fifth metatarsals. When appropriately balanced, the TMA can provide a functional foot.

Lisfranc Amputation

A Lisfranc disarticulation should be considered when there is inadequate soft tissue coverage for a Transmetatarsal amputation.

Chopart’s Amputation

The Chopart’s amputation is a disarticulation through the midtarsal joint, leaving only the talus and calcaneus. Patients requiring a Chopart’s amputation often present with infection extending proximally to the midfoot. Compared to below-knee or Syme’s amputations, it has some advantages: it is possible to use a shoe with a specific filler, avoiding a leg prosthesis, as for the other two amputations, it does not cause limb shortening.
Syme’s Amputation

A Syme’s amputation involves a disarticulation of the ankle joint. This amputation preserves function of the knee with a long stump and independence by allowing patients to expend less energy walking than patients with higher-level amputations.[14]

Partial Calcanectomy

In cases of forefoot and midfoot pathology necessitating amputation, the calcaneus is maintained after removing the talus, and fused to the distal tibia. This gives stability and maintains some length to the remaining limb, preserves the distal flap and plantar fat pad. A partial calcanectomy is an alternative to below-knee amputation for calcaneal osteomyelitis with overlying tissue loss. Once healed, most patients maintain ambulation and improved quality of life is achieved by preserving a functional limb. Patients are generally kept non-weight-bearing for a period of 6 weeks and then fitted for accommodative footwear.[15]

Quality of Life

Major amputations are done when the ulcerated foot either threatens patient survival or when reasonable function can no longer be expected. However, an inappropriately conservative approach could conceivably enhance suffering by condemning a person to months of incapacity before they die with a non-healed ulcer. The consideration of the quality of life in patients with non-healed ulcers or different levels of amputation is, therefore, of importance. With non-healing ulcers, diabetic patients run a high risk of depression.[16]

Prevention of diabetic foot ulcers

Diabetic ulcers of lower extremity are a chronic problem with significant recurrence rates. Therefore, long-term maintenance must be addressed even for healed ulcers.

This includes identification of high-risk patients, education of the patient, and institution of measures to prevent ulceration. High-risk patients should be identified during a routine foot examination performed on all patients with diabetes.[19]

Patient education should emphasize careful selection of footwear, daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma, daily foot hygiene to keep the skin clean and moist, avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and prompt consultation with a health care provider if an abnormality arises. Any diabetic patient admitted to acute care setting should have their feet examined on admission. Patient education and self-care practices like maintaining foot hygiene and nail care should be promoted. Skin should be kept moisturized with the application of topical moisturizers after washing the feet gently with soap and water.[17]

Early detection of potential risk factors for ulceration can decrease the frequency of wound development. It is recommended that all patients with diabetes undergo a foot examination at least annually, to determine the predisposing conditions to ulceration. Patients should be educated regarding the importance of maintaining good glycemic control, wearing appropriate footwear, avoiding trauma, and performing frequent self examinations.[18] Diabetic foot ulcers (DFU) are chronic complications due to poor diabetic control. Diabetic foot ulcers can lead to lifelong disability and substantially diminish the quality of life.

Clinical Pharmacist Roles in the management of diabetic foot ulcer care:[20]:

- Develop, evaluate and document pharmaceutical care practices in DFU.
- Collaborate with other health care professionals to develop treatment guidelines for DFU.
- Educate all health professionals who participate in pharmaceutical care.
- Participate in health screening for diabetes, and DFU (HbA1c, FBS, PPBS, etc.).
- Conducting health promotion and education programs for smoking cessation, obesity control, DFU self-practice, DFU preventive measures DFU awareness camp etc.
- Educate and collaborate community pharmacist and their services in the prevention and management of DFU.
- Referral for management from counseling centers and community pharmacies.
Research in the field of pharmacotherapeutics pharmacoepidemiology; pharmacy practice; health economics in diabetes and DFU.

To evaluate and document the results of research in order to improve all aspects of pharmaceutical care.

Participate in the formulation of antibiotic policy and its regulations.

To Develop professional standards and audit procedures.

Conclusion

Diabetes is a chronic disease associated with various diseases. The diabetes confers with increase risk of foot ulcer. The risk reduction depends on appropriate screening and intervention measures are required. The recommendation should be reinforced that proper reviewing past history, Physical examination, identifying foot deformities is required. Proper Monitoring blood sugar levels, Patient education, wound debridement, advanced dressing, surgery and advanced therapy and appropriate footwear practices, advanced clinical care practice, individual self care practice will helpful for reducing the risk of foot infection. It is essential that carefully and completely training the patients and preventive measures as well as foot care will hope for preventing the progress of foot ulcers.

Pharmacists utilize their clinical expertise in monitoring and managing diabetes medication plans to positively impact health outcomes and empower patients to actively manage their health. In addition, pharmacists can serve as a resource to other health care providers and payers to assure safe, appropriate, cost-effective diabetes medication use\[20\].

References