International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.9, pp 843-851, 2017

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% reoccurrence 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 behavioralpatterns. 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,pressureand 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 factorsdiabetic retinopathy and nephropathy and anatomicaldeformities, environmental factors peripheral vascular disease.

Pathophysiology

Diabetic foot ulcers are chronic wounds that failto heal in a regulated and systematic manner due to multipleabnormal 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 regulationof the cytokines, growth factors, proteases, extracellularmatrix components, and cells needed to achievecomplete wound closure. Thekeratinocyte migration andproliferation is impairedand fibroblast response to growthfactorsand the ability to synthesize collagen is impaired.

There is a relative deficiency of tissue inhibitorsof matrix metalloproteinases, which results in degradation of the extracellular matrix [9].All these pathophysiologicfactors contribute to the poor healing rates observed inpatients with Diabetic foot ulcers.

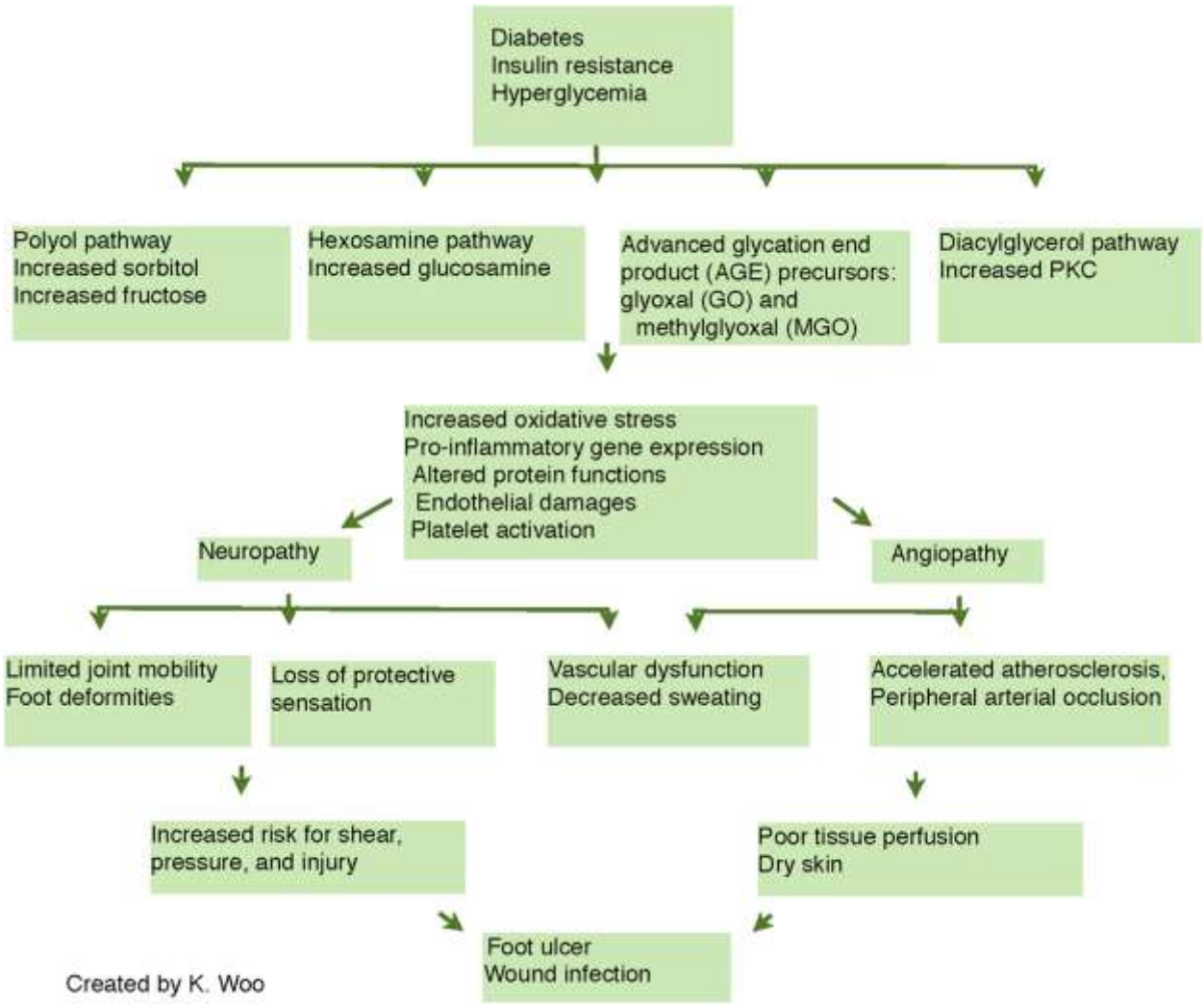

Fig 1: Pathophysiology of Diabetic foot ulcer

Classification of diabetic foot ulcers

Several schemes have been used to classify diabetic foot ulcers, but none of them hasbeen 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 DFUsin six grades based on the wound's depths and extent of gangrene.

Table: 1 Wagner Classification of Diabetic Foot Ulcer

Grade 0	No ulcer in a high risk foot
Grade 1	Superficial ulcer involving the full skin thickness but notunderlying tissues.
Grade 2	Deep ulcer, penetrating down to ligaments and muscle, but nobone involvement or abscess formation.
Grade 3	Deep ulcer with cellulitis or abscess formation, often withosteomyelitis.
Grade 4	Localized gangrene.
Grade 5	Extensive gangrene involving the whole foot.

The University of Texas Wound Classification

The University of Texas classification is a more comprehensive scale and includes riskstratification and expresses tissue breakdown, infection and gangrene separately.Although Texas classification describes the grade of wound in more details, it does notinclude measures of neuropathy or ulcer area [11].

Table: 2 The University of Texas Wound Classification System

Stage	**Grade**			
	0	**I**	**II**	**III**
A	pre- or post ulcerative completely epithelized lesion	Superficial wound	Woundpenetration uptotendon or capsule	Wound penetration up to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

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

Another validated classification system for DFUs that includes the severity of infection isThe PEDIS (perfusion, extent, depth, infection, and sensation) system.1 PEDISclassification was proposed by the International Working Group on the Diabetic Footand 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 thesefactors. The in-depth nature of this system is appropriate for the research communitythat desires this amount of detail.

Table3:The International Working Group on the Diabetic Foot risk categorization tool

Category	Risk factor
0	No sensory neuropathy
1	Sensory neuropathy
2	Sensory neuropathy and foot deformity
3	Previous ulcer or amputation

Treatment

General Management

Management of DFUs is complex andrequires a systematic approach to achievemore consistent and successful outcome.This includes addressing multiple issues like treat in 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 areinvolved so infection [12,13] should be considered polymicrobial.Appropriate wound swab cultures or bone biopsy culturesshould be required for proper management of infection. For mild, soft tissue infection, oral antibiotics are good enough.Moderate to severe infectionsrequire parenteral, combination therapy.The use of topicalantibiotics is usually not recommended. The prevention of infection is not achieved throughthe use of medications but could be achieved with patienteducation; foot hygiene, proper protection of pressure pointsand early local care of shallow ulcers.

Infection Severity	Probable Pathogen(s)	Antibiotic Agent
Mild (usually treated with oral agent[s])	Staphylococcus aureus (MSSA); Streptococcus spp	Dicloxacillin clindamycin Cephalexin Levofloxacin Amoxicillin-clavulanate
	Methicillin-resistant S. aureus(MRSA)	Doxycycline Trimethiprim/sulfamethoxazole
Moderate[may be treated with oral or initial parenteral agent(s)]	MSSA; Streptococcus spp; Enterobacteriaceae; Oblicate anaerobes	Levofloxacin Cefoxitin Ceftriaxone Ampicillin-sulbactam Moxifloxacin Ertapenem Tigecycline Levofloxacinor ciprofloxacinwith clindamycin Imipenem-cilastatin
	MRSA	Linezolid Daptomycin Vancomycin
	Pseudomonas aeruginosa	Piperacillin-tazobactam
	MRSA, Enterobacteriacae, Pseudomona and Obligate anaerobes	Vancomycinplus one of the following: Ceftazidime, Cefepime, piperacillin-tazobactam, aztreonam, or a carbapenem

Ulcer Care

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

Ulcer surgery

Chronic ulcers are the resultof prolonged biological hazards. Therefore, good outcomesare measured in weeks and months rather than days. At leastsix to ten weeks is the expected time for healing of thesecomplicated lesions. Breakdown of splitskin-grafted areas is common with daily ambulation and footwearpressure.

Surgery to Facilitate Ulcer Healing

Chronic diabetic foot ulcers combined with functional problemsadd further risks to the formation of more ulcers. Suchsituations can arise when the Achilles tendon becomes tight asa result of prolonged disuse of the ankle. The plantar flexedankle imposes more pressure on the metatarsal heads whichmay be responsible for pressure ulcer development. The tightAchilles tendon can be lengthened, so as to release metatarsalhead pressure. After the lengthening, there is an initial weakeningof 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 viaseparate incisions.The diabetic patient with chronic ulceration of the footoften has co-existing deformities which might need to be correctedto prevent ulcer recurrence or new ulcer development.Surgery may involvejoint fusion at the site of the arthropathy or in the most unstablelate cases, amputation.

Supportive Treatment

Abnormal pressure points undoubtedly predispose thediabetic foot to ulceration. Protecting the pressure points,therefore, becomes vital for the prevention of ulcer formation.However, most diabetic ulcers are complicated by peripheralarterial disease and infection[11].Therefore, pressure relievingdevices are important mostly after treatment interventionsand ulcer healing.

Oxygen therapy

Oxygen therapy, for the majority of people, is also known ashyperbaric oxygentreatment.The pressure around thelimb is kept just above atmospheric pressure. Topical oxygenwill 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 thehallux with the flexor hallucislongus 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 forefoot instability, not only because of the digitigrades contributionduring 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 thestep and the loss of plantar-flexion of the toe, a collapse of the medial column with apossible evolution towards a pronated and valgus foot. It may also lead to ulcerativelesions or stress fractures of the other rays.It is important to keep the insertion of the anterior tibial tendon and peroneus longustendon on the metatarsus, leaving a functionally valid foot, if necessary with the use ofan 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 lesionsor stress fractures.

Transmetatarsal Amputation

Transmetatarsal amputation (TMA) is typically performed in patients with chronicosteomyelitis involving the forefoot, gangrene of the toes, or a non-healing ulcerationwith a previously resected first-ray. As mentioned earlier, a first-ray resection altersnormal gait characteristics and patients are at higher risk for developing transfer lesions,putting them at risk for subsequent amputation. The resection of multiple central raysresults in a nonfunctional 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 theareas of attachments of tibialis anterior and peroneus brevis on the first and fifthmetatarsals. 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 onlythe talus and calcaneus. Patients requiring a Chopart's amputation often present withinfection extending proximally to the midfoot[12].Compared to below-knee or Syme's amputations[19],it has some advantages: it is possibleto use a shoe with a specific filler, avoiding a leg prosthesis, as for the other twoamputations, 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 patientsto expend less energy walking than patients with higher-level amputations [14].

Partial Calcanectomy

In cases of forefoot and midfoot pathology necessitating amputation, the calcaneus ismaintained after removing the talus, and fused to the distal tibia.This gives stability andmaintains some length to the remaining limb, preserves the distal flap and plantar fatpad. A partial calcanectomy is an alternative to below-knee amputation for calcanealosteomyelitis with overlying tissue loss. Once healed, most patients maintainambulation 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 fittedfor accommodative footwear [15].

Quality of Life

Major amputations are done when the ulcerated foot eitherthreatens patient survival or when reasonable function can nolonger be expected.However, an inappropriately conservativeapproach could conceivably enhance suffering by condemninga person to months of incapacity before they die with a non-healedulcer. The consideration of the quality of life in patientswith non-healed ulcers or different levels of amputation is,therefore, of importance.With non-healing ulcers, diabetic patients run a high risk ofdepression [16].

Prevention of diabetic foot ulcers

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

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

Patient education shouldemphasize careful selection of footwear, daily inspection of the feet to detect early signsof poor-fitting footwear or minor trauma, daily foot hygiene to keep the skin clean andmoist, 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 abnormalityarises. Any diabetic patient admitted to acute care setting should have their feetexamined on admission. Patient education and self-care practices like maintaining foot hygiene and nail careshould be promoted.Skin should be kept moisturized with the application of topicalmoisturizers after washing the feet gently with soap and water [17].

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

Clinical Pharmacist Roles in themanagement 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 theirservices in the prevention andmanagement of DFU.
- Referral for management from counseling centers andcommunity 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 orderto improve all aspects of pharmaceutical care.
- Participate in the formulation of antibiotic policy and itsregulations.
- To Develop professional standards and audit procedures.

Conclusion

Diabetes is a chronic disease associated with various diseases. The diabetes is 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].

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