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Diabetic Foot Ulcer: An Easy and Comprehensive Approach

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Abstract

Foot problems are commonly involved in diabetes, and the most common presentation of diabetes is an ulcer. Diabetic foot ulcer is a complex problem caused by reduced blood supply, nerve damage, or infection. But unfortunately in most of cases, these three factors have played a role for impairment of diabetic feet. Sometimes nerve damage or neuropathy is an initial insult, and multiple times ischemia is the leading factor for ulcer formation. After certain period, infection finally supervenes and makes a sterile ulcer to infected leads to loss of limb or foot. This becomes more complicated because of less pronounced ischemic symptoms in diabetic than non-diabetics. Furthermore, the healing of a neuroischemic ulcer is slowed down by microvascular dysfunction. Therefore, some ulcers can get better by revascularization, but pure ischemic ulcers rarely respond to revascularization. Many guidelines have largely ignored these specific demands related to ulcerated neuroischemic diabetic feet. Any diabetic foot ulcer should always be considered to have vascular impairment unless otherwise proven. This chapter highlights the best way to diagnose and treat these patients with diabetic foot ulcer. Most of the studies dealing with neuroischemic diabetic feet are not comparable in terms of patient populations, interventions, or outcomes. Therefore, there is an urgent need for a paradigm shift in diabetic foot care, that is, a new approach and classification of diabetics with foot ulcer in regard to clinical practice and research.

Keywords: diabetic, ulcer, Hyderabad, diabetic foot, diabetic foot ulcer, revascularization

1. Introduction

Diabetic foot ulcer is a late and disfiguring complication, which leads to higher risk of amputation of any part of the foot or leg. Therefore diabetic foot disease has major medical, economic, and social consequences. It is very important to treat it with proper protocol to save patients from fatal and disabling complications.

The complexity is to understand the main insult which can be diabetic peripheral arterial disease, neuropathy, or infection. The healing process is also halted due to impaired collagen synthesis. Vascular disease varies from arteritis, occlusion, and large vessel atherosclerosis.

The diabetic foot ulcer is a cave of infection, severe vessel ischemia, and multiple painless traumas. Factors that exacerbate the problem are advanced age, duration of the diabetes, and control of diabetes.

Diabetic foot ulcers are classified in many ways, but many systems of classification are complex to interpret. Hence, particular attention to feet care should be a central focus in educating and managing patients with diabetes to ensure that ulcer is either prevented or noticed early enough.

2. Classification and epidemiology of diabetes and foot ulcer

Persistent elevation of blood sugar is associated with major metabolic abnormalities in diabetic patients and damages to various organs and systems, leading to life-threatening complications, which can be overt like major cardiovascular events and cerebrovascular accidents or covert such as retinopathy or nephropathy.

Diabetes mellitus is broadly classified into four types by etiology and clinical presentation, type 1 diabetes, type 2 diabetes, gestational diabetes (GDM), and other less common types of diabetes, which include monogenic diabetes and secondary diabetes.

1. Type 1 diabetes, which involves autoimmune beta-cell destruction, leads to absolute insulin deficiency.

In the past decade, there was a 21% increase in the number of type 1 diabetes in the USA [1], and the prevalence is increasing at a rate of 3% per year globally [2]. Another study reported that the annual increase was 2% in type 1 diabetes and 5% for type 2 diabetes [3].

There is no gender variation in type 1 diabetes [4], and type 1 diabetes reduce life expectancy by 13 years as per data reported [5]. Approximately 15% of adults to diagnosed with type 2 diabetes have actually latent autoimmune diabetes of adults, which are a variant of type 1 diabetes [6].

2. Type 2 diabetes (steady loss of beta-cell insulin secretion or insulin resistance).
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy).
4. Specific types of diabetes due to other causes:
 - maturity-onset diabetes of the young [MODY] or neonatal diabetes;
 - diseases of the pancreas, for example, cystic fibrosis and chronic pancreatitis; and
 - drug- or chemical-induced diabetes.

Nearly 463 million adults (20–79 years of age) are living with diabetes; by 2045, this will rise to 700 million. The proportion of people with type 2 diabetes is increasing in most countries, and 79% of adults with diabetes are living in low- and middle-income countries. The greatest number of people with diabetes is between 40 and 59 years of age.

In past year, subcontinents were affected enormously. It was estimated that nearly 20 million adults in Pakistan were diabetics, putting them at risk for major or minor complications, and approximately 8 million are still undiagnosed [7].

There are many contributing risk factors for type 2 diabetes: poor socioeconomic status, reduced literacy in 41%, low occupation in 31%, and less income in 40% [8].

More than 15% of diabetic people during their lives experience foot ulcers [6]. These ulcers account for more than 80% of nontraumatic lower limb amputations [9]. The burden of foot ulcer in diabetes varies from 3% in Oceania to 13% in North America, Canada (14.8%), Asia 5.5%, and Europe 5.1% [10].

The annual incidence of diabetic foot ulcer or necrosis in diabetic patients is known to be about 2–5%, and the lifetime risk ranges from 15 to 20% [11].

3. Risk factors for diabetic foot ulcer

Males are affected more than females, and it is more common in **the elderly** above 60 years of age. Several studies have reported **racial predisposition**. One author has evaluated that the increased risk of amputation in African blacks was 2- to 3-fold higher than that in whites [12].

The diabetic foot ulcer is seen in **lower socioeconomic** class (78.2%) [13]. **Smoking** aggravates macrovascular complications including peripheral arterial disease.

It has been observed that 47% of patients who had previous ulceration **walked barefooted** within the house and 17% walked barefooted outside [14]. **Neuropathy** was involved in more than half of diabetic foot ulcers [15], while **peripheral vascular disease** accounts for about 15% alone and 35% in conjunction with neuropathy. The **unequilibrated distribution of pressure** in the foot during walking exposes pressure bearing points to ulceration [16]. The **previous foot ulcers** have tendency to develop recurrent diabetic foot ulcers.

Previous amputation is undoubtedly a big risk factor in 50% of the diabetic foot ulcers. **Inappropriate footwear**s produce foot ulcer frequently in diabetes. **Poor vision** contributes due to diabetic retinopathy with the patient unable to properly identify injurious objects. **Minor or major trauma to foot** could be an origin of a chronic ulcer or wound.

4. Pathogenesis of diabetic foot ulcer

It is a worst combination of neuropathy and ischemia. It becomes more complicated by infection. This process leads to impaired wound healing, decreased cell growth factor response, reduced tissue perfusion, and decreased local angiogenesis.

The precise pattern of diabetic neuropathy is not yet completely understood. More evidence has identified the polyol pathway as a major factor in diabetic neuropathy, which leads to oxidative injury. It becomes more complicated when combined with osmotic cell-induced nerve damage, which triggers nerve cell edema. More than half of foot ulcers were caused by neuropathy [17].

Multiple neuropathies are involved in diabetic foot ulcer, which cause impaired pain sensation and impaired temperature sensation. Sensory diabetic neuropathy increases incidence of ulcer at foot approximately sevenfold, compared to diabetic patients without sensory neuropathy [18].

Finally ulcer appeared which may become chronic and combined to atrophy of foot muscles, flexion extension imbalance and also impaired equilibrium. Progressively, repeated pressure at focal points within the foot leads to ulceration. Furthermore, there is reduced sweating and dryness of the skin predisposing to cracks, which become potential sites for frequent ulceration and portals for bacterial entry.

Peripheral arterial disease is a macrovascular complication and an essential contributor to diabetic foot. The endothelial dysregulation that occurs in diabetes

leads to reduced production of nitrous oxide (NO), which is a dependable vasodilator and regulates smooth muscle proliferation and leucocyte adhesion, resulting in atherosclerosis and vascular narrowing and ischemia.

The limb or foot ischemia can happen even in the presence of palpable pedal pulses [19].

Also, hyperglycemia promotes increased levels of fibrinogen and plasminogen activator inhibitor which impairs fibrinolysis [20]. These and other abnormalities promote platelet adhesion and thrombosis. In addition, the formation of advanced glycation end products which are compounds formed by the nonenzymatic reaction between sugars and proteins leads to cross linking of molecules in the extracellular matrix of the basement membrane. This alters the structure of the vessels and promotes stiffness [21]. There is also an increased expression of growth factors and adhesion molecules, e.g., intracellular adhesion molecule 1 and vascular endothelial growth factor [22]. Dyslipidemia also contributes to atherosclerosis. In fact, a 1% increase in HbA1C is related to 25–28% of relative risk of peripheral arterial disease [23–26].

Wound healing is defective in diabetes partly due to deficient angiogenesis. It has been noticed that abnormal excessive and inadequate angiogenesis occurs with diabetic complications, delayed closure time, and impaired tissue remodeling [27]. The inadequate mobilization of bone marrow-derived endothelial progenitor cells (EPCs) to the site of injury is another possible mechanism of impaired healing. These cells respond to ischemia and populate the injury site where they form new vessels [28].

About 60% of diabetic foot ulcers have been infected which could be superficial, deep, or more complex such as osteomyelitis [29]. Although typical signs and symptoms could be absent, severe infection could present with systemic symptoms, e.g., fever, chills, and tachycardia. The Infectious Diseases Society of America (IDSA) criteria for severe diabetic foot infection are temperature of $>100^{\circ}\text{F}$, tachycardia, tachypnea or respiratory alkalosis, leukocytosis, or leucopenia [30]. The commonly isolated organisms are *Staphylococcus aureus*, *S. epidermidis*, and *Streptococcus* species. Methicillin-resistant *S. aureus* (MRSA) complicates 32% of infections, and it is associated with treatment failure. Among anaerobes, *Peptostreptococcus magnus* and *Bacteroides fragilis* have been isolated. The majority of cases are polymicrobial. *S. aureus*, Group B *Streptococcus*, and gram-negative *Bacilli* are associated with limb-threatening infections [31].

5. Classification of diabetic foot ulcer

Wagner classification system: This system focused on physical characteristics of ulcer, depth, and the presence of osteomyelitis or gangrene (0–5) [32].

SINBAD assesses site, ischemia, neuropathy, bacterial infection, and depth and uses a scoring system 0–6. It has been focused on clinical and gross pathological changes of ulcer.

PEDIS classification: This system was designed by the International Working Group on the Diabetic Foot and uses the same five components of S(AD) SAD: perfusion, extent, depth, infection, and sensation. It does not include ulcer location [33].

DEPA classification: This system looks at four aspects of ulcers: depth, extent of bacterial colonization, phase of healing, and associated etiology. Each category is scored from 1 to 3 according to severity.

University of Texas has been proven effective at predicting lower extremity amputation when combined with Wagner classification, and it comprises four grades, A to D, and four stages, 1–4 [34].

Kobe’s Classification focused on neuropathy, infection and vasculopathy: Type 1, mainly peripheral neuropathy (PN); type 2, mainly peripheral arterial disease (PAD); type 3, mainly infection; and type 4: all three combined, neuropathy, peripheral arterial disease with infection [35].

SAD stands for sepsis, arteriopathy, and denervation system. The major drawback of this classification is that it is potentially complex and is primarily intended for selecting population for prospective research [36].

Diabetic Ulcer Severity Score (DUSS)

The Diabetic Ulcer Severity Score (DUSS) is based on the categorization of wounds into specific severity subgroups for a comparison of outcomes. Assessment using the DUSS system includes the presence of pedal pulses, the ability to probe to the bone within the ulcer, and ulcer quantity and location. The sum of points determines severity, with the score ranging from 0 to 4.

6. Approach to diabetic foot ulcer

Feature	Neuropathic	Ischemic	Neuroischemic
Sensation	Sensory loss	Pain	Degree of sensory loss
Callus/necrosis	Callus present	Necrosis common	Minimal callus; prone to necrosis
Wound bed	Pink and granulating, surrounded by callus	Pale and sloughy with poor granulation	Poor granulation
Foot temperature and pulses	Warm with bounding	Cool with absent pulses	Cool with absent pulses
Other	Dry skin and fissuring	Delayed healing	Risk of infection
Typical location	Weight-bearing areas of the foot, such as metatarsal heads, the heel, and over the dorsum of clawed toes	Nail edges and between the toes and lateral borders of the foot	Margins of the foot and toes
Prevalence	35%	15%	50%

7. Assessment of risk

Risk category 0 [37]	Risk category 1	Risk category 2	Risk category 3
Norma plantar sensation	Loss of plantar sensation	Loss of plantar sensation or poor circulation or foot deformity or onychomycosis	History of ulceration, neuropathic fracture, or amputation
Low risk	Moderate risk	High risk	Very high risk

8. Investigations

- CBC
- Renal function tests
- CRP and ESR

- Blood sugar levels
- HbA1C
- Blood culture and sensitivity
- X-ray of the foot [38]
- MRI of the foot
- PET scan in osteomyelitis [39]

Ankle brachial index: in normal subjects, the ankle systolic pressure is higher than the brachial systolic pressure. The normal ABI > 1; in the presence of ischemia, it is <0.9. Absent or feeble pulses, with ABI < 0.9, confirm ischemia [40].

Transcutaneous oxygen tension method TcPO2 less than 20 mmHg has been associated with early wound healing failure [41].

- Ultrasound Doppler vascular studies
- CT angiogram

9. Diabetic foot examination

Sensory examination	Vascular examination	Deformity	Ulcer examination
Vibratory perception: 128 Hz tuning fork or electronic tuning fork	Pedal pulses: dorsalis pedis, posterior tibial, perforating peroneal	Bunions, hammertoes, bone spurs, plantarflexed metatarsals, pes cavus foot type	Area, toe, metatarsal forefoot, lateral, medial
Achilles reflex	Erythema or cyanosis	Hallux limitus, Achilles/ gastro equinus, overpronation	Ischemic or neuropathic or mixed
Monofilament test 10 point touch [42]	Intermittent claudication score	Rocker bottom appearance	Small <10 cm, moderate 11–40 cm, severe >40 cm
Vibration perception threshold (VPT)	Temperature comparison between feet	Prior amputation	Cool with absent pulses
Temperature sensation	Dry skin and fissuring	Gait evaluation	Depth; probe test
Pain sensation	Vascular Doppler ultrasonography	Foot drop, atrophy, necrobiosis lipoidica diabeticorum	Healing or nonhealing (inflammatory granulating epithelialization)

10. Treatment

Treating diabetic foot ulcer is an art and involves multiple specialties. The essential team members are physicians, chiroprapist, orthopedics, radiologist, and

vascular surgeon. The focus would be ensuring targeted HbA1c, revascularization, wound healing with or without debridement, shading of excessive load over foot or limb, and limiting infection by antibiotics and assessment of complications. Focus on the patient's education and nutrition is very important in reducing recurrence of diabetic foot ulcer.

10.1 Offloading

It means reduction, redistribution, or sharing pressures over the ulcer area. It is a well-known fact that offloading is one of the cornerstones of successful diabetic foot ulceration management and prevention. The aim is to reduce the plantar pressure by redistributing it to a larger area, to avoid shear and friction, and to accommodate the deformities [43].

For diabetic foot ulcer, a proper cast is necessary; for example, nonremovable cast devices are the most clinically effective for neuropathic forefoot and mid-foot ulceration. The aim is to immobilize the foot and ankle within the cast, which significantly reduces shear force.

The total contact cast is a below-knee cast that encroaches the lower limb, encasing the whole foot. It is the main cast for mid- and forefoot lesions and for neuropathic noninfected plantar ulcers. Healing was reported in almost 100% cases of ulcers within 5–8 weeks. For non-cast offloading devices, half shoes are designed to offload either the fore or rear foot. We can decide by giving examples below about casting devices:

Rear foot

For weight-bearing:

Crutches with or without a below-knee cast and a half shoe.

For non-weight-bearing:

Leg trough, pressure-relieving mattress and flexible heel cast or pillows.

Mid-foot

Total contact cast, below-knee cast, or fiberglass boot. Felt padding can be shaped to cover the sole of the foot with a cavity at the ulcer site.

Forefoot

Half shoe; leg- or boot-type cast is the most effective method for offloading; sandals with a foam-filled sink in the sole unit located over the ulcer site may also be useful.

Toe

Cut a hole in the part of the shoe overlying the ulcer site to remove the whole toe from shoe.

A recent systematic review has found nonremovable offloading devices like total contact cast to be more effective for ulcer healing than removable offloading devices [44].

11. Control of foot infection

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscle, joints, and bones [45, 46].

First-generation cephalosporin, clindamycin, fluoroquinolone, linezolid.

Moderate infection without systemic involvement.

Ticarcillin/clavulanate, piperacillin/tazobactam; second- or third-generation cephalosporin.

Third-generation cephalosporin, imipenem.
Ugly ulcer with systemic signs.
Ticarcillin/clavulanate, piperacillin/tazobactam; + ceftazidime, flucloxacillin + cipro, carbapenem.
Ischemic limb/necrosis/gas forming.
Ticarcillin/clavulanate, piperacillin/tazobactam or carbapenem; second-/third-generation cephalosporin + clindamycin or metronidazole.

12. Control of ischemia

Revascularization surgery: Patients with peripheral ischemia who have significant functional disability should undergo surgical revascularization if medical management fails. This may decrease the amputation risk in patients with ischemic DFUs.

The procedures include open (bypass grafting or endarterectomy) or endovascular techniques (angioplasty with or without stent) [47].

Extracorporeal shock wave therapy acts by increasing angiogenesis and blood supply and cellular proliferation and thus hastening wound healing.

Low-energy lasers have also been used as an adjunctive therapy for DFUs [48].

13. Wound debridement

Ulcers heal more quickly if the surface is clean; physicians must debride impediments to healing, such as necrotic tissue and bacteria. The popular strategy is to do sharp debridement. So removal of necrotic tissue often extends beyond the ulcer bed, and some authorities have recommended to debride deeper tissues also.

Other strategy is to convert bad ulcer to fresh ulcer by excise the already an ulcer, underlying bony prominences. Good results have been reported with this approach [49].

Many other strategies of debridement include physical debridement using wet-to-dry dressing, enzymatic debridement using enzymes like collagenase and papain as ointment preparations, autolytic debridement with the use of moisture-retaining dressings, and biological debridement with the use of larvae of common green bottle fly [50].

14. Wound dressings

Dressings can provide a warm, moist environment required for healing after debridement. Common problems associated with some of these dressings have been dehydration of the ulcer bed, saturation with exudate, and/or the failure to properly apply antibiotics and growth factors needed to promote angiogenesis and granulation tissue. Non-medicated dressings include paraffin gauze, while medicated include Xeroform [51].

Dressing materials include saline-moistened gauze dressings (wet-to-dry), moisture-retaining and antiseptic dressings, silver dressings, and cadexomer.

Chemically treated honey can be used alone or in combination with sterile dressings [52].

In terms of ulcer healing, a meta-analysis of trials in which people with neuropathic foot ulcers received good wound care reported that 24% of ulcers attained complete healing by 12 weeks and 31% by 20 weeks.

In highly exuding ulcers, dressing is essential in managing the high volume of exudate, achieving moisture balance and preventing peri-wound soft tissue damage. The frequency of wound dressing change is important in achieving these goals.

Superabsorbent dressings are designed to absorb high volumes of wound exudate and to hold and lock the fluid into the structure of the dressing, which may reduce the need for frequent dressing changes.

In a wound with low exudate levels, which contains slough, dressings should be selected with the aim of increasing wound moisture to aid autolysis and achieve moisture balance. In the case of black, dry, and necrotic toes due to ischemia, the primary goal is to keep the toe dry, prevent infection, and protect adjoining or adjacent issues.

15. Nutrition and diabetic foot ulcer

As the other factors are important for proper care of diabetic foot ulcer, nutrition has a pivotal role in healing, prevention of recurrence, and fair outcome. Unfortunately, it is a least considered part of diabetic foot ulcer management.

Imran et al. have shown that BMI was significantly associated with severity of ulcer; BMI of 29 was associated with grade 1 ulcer and low BMI of 23 with grade 5 foot ulcer. Over Mini nutritional assessment scale, a score less than 23.5 was associated with advanced foot ulcers, score < 17 was associated with significant p value < 0.03, and score in between 17 and 23.5 was associated with p value of 0.05 [53].

16. Charcot arthropathy

Charcot neuroarthropathy, or Charcot foot, is a complication of diabetes mellitus where there is progressive degeneration of the joints. It commonly affects the middle of the foot, hindfoot joints, the ankle, and forefoot joints, and it is believed to result from inflammation in the tissues. The prevalence of Charcot neuroarthropathy is approximately 13% with diabetes [54].

Charcot neuroarthropathy could result in ulceration and infection which can lead to amputation of the limb. Early recognition and intervention is imperative to avoid the rapid progression toward permanent foot deformity, ulceration, and the possibility of limb loss. Once it has started, ongoing inflammation leads to bone deformities.

The acute Charcot arthropathy results in bony reabsorption and multiple spontaneous fractures. Charcot joint changes can be classified into stages.

0 (prodromal): Elevated temperature, with or without foot edema and bounding pulses. The X-ray of foot is less helpful.

1 Developmental, acute: An acute destructive period that is induced by minor trauma resulting in fragmentation of bone and joint dislocation and subluxation. This stage should be verified by a physician early; otherwise, misdiagnosis will lead to permanent deformities.

2 Subacute: The patient presents with decreased edema and healing of fractures.

3 Chronic: Healing, deformity and remodeling of bones seen on x-ray.

The acute phase is often misdiagnosed and can lead to permanent foot deformity and ulceration, thus increasing the risk of lower extremity amputation [55].

There are three types of Charcot foot classification: clinical, anatomical, and radiological. In clinical practice, Charcot foot can be classified into the acute and chronic stages [56].

The best way to deal with this stage is offloading of the foot, avoid weight-bearing, prevention of aim of chronic deformities. The pain must be reduced managed and assessment of disease activity by physical signs, X-rays or C reactive protein.

The surgery is indicated for correction of deformities. One researcher has been followed up 100 patients for a median of 3.8 years after conservative treatment for Charcot foot [27] and noted amputations in 2.7% and ulcer recurrence in 49%, but some of them have been prevented by earlier surgical intervention [57].

17. Conclusion

Diabetic foot ulcer contributes to be a major cause for morbidity in patients despite of multiple, advanced, and suitable interventions at different levels. This problem could be addressed and managed by encouraging the patient's education, especially to foot care.

Patients should be motivated to care better for themselves by getting involved in learning programs, which highlight the risk factors and consequences of diabetic foot. These patients should be taught in the simple way to examine an ulcer and assess modified risk factors. The synthesis of national and local guidelines on diabetic foot care should be a priority, and the adherence to such guidelines has to be monitored by concerned organizations.

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References

- [1] Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*. 2014;**311**:1778-1786
- [2] Cho NH, Whiting D, Forouhi N, et al. IDF Diabetes Atlas. Diabetes in Children. 2015;**7**:14-16
- [3] Mayer-Davis E, Lawrence JM, Dabelea D, et al. Incidence trends of Type 1 and Type 2 diabetes among youths. *NEJM*. 2017;**376**:1419-1429
- [4] Maahs DM, West NA, Lawrence JM, et al. Epidemiology of type 1 diabetes. *Endocrinology and Metabolism Clinics of North America*. 2010;**39**:481-497
- [5] Livingstone SJ, Levin D, Looker HC, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. *JAMA*. 2015;**313**:37-44
- [6] Stenström G, Gottsäter A, Bakhtadze E, et al. Latent autoimmune diabetes in adults: Definition, prevalence, β -cell function, and treatment. *Diabetes*. 2005;**54**:S68
- [7] Cho NH. Estimates of diabetes for projections to 2030 and 2045. IDF Diabetes Atlas. 2019:9-10. Available from: <http://doi.org/10.1016/j.diabetes.2019.107843>
- [8] Allebeck P, Hallqvist J, Moradi T, et al. Type 2 diabetes incidence and socio-economic position: A systematic review and meta-analysis. *International Journal of Epidemiology*. 2011;**40**:804-818
- [9] Trautner C, Haastert B, et al. Incidence of lower limb amputations and diabetes. *Diabetes Care*. 1996;**9**:1006-1009
- [10] Zhang P, Lu J, Jing Y, Tang S, Zhu D, et al. Global epidemiology of diabetic foot ulceration: A systematic review and meta-analysis. *Annals of Medicine*. 2017;**49**:106-116
- [11] Khanolkar MP, Bain SC, Stephens JW. The diabetic foot. *QJM*. 2008;**101**(9):685-695
- [12] Leggetter S, Fuller JH, et al. Ethnicity and risk of diabetes-related lower extremity amputation. *Archives of Internal Medicine*. 2002;**162**(1):73-78
- [13] Adeleye JO. Diabetic foot disease: The perspective of a Nigerian tertiary health care center. *Practical Diabetes International*. 2005;**22**(6):211-214
- [14] Gulliford MC, Mahabir D. Diabetic foot disease and foot care in a Caribbean community. *Diabetes Research and Clinical Practice*. 2002;**56**(1):35-40
- [15] Dyck PJ, Davies JL, Wilson DM, Service FJ, et al. Risk factors for severity of diabetic polyneuropathy: Intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study Cohort. *Diabetes Care*. 1999;**22**:1479-1486
- [16] Kruse I, Endelman S. Evaluation and treatment of diabetic foot ulcers. *Clinical Diabetes*. 2006;**24**:91-93
- [17] Clayton W, Elcasy TA. A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. *Clinical Diabetes*. 2009;**27**:52-58
- [18] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;**27**:1047-1053
- [19] Armstrong DA, Lavery LA. Diabetic foot ulcers: Prevention, diagnosis and classification. *American Family Physician*. 1998;**57**:1325-1332
- [20] Vinik AI, Erbas T, et al. Platelet dysfunction in type 2 diabetes. *Diabetes Care*. 2001;**24**(8):1476-1485

- [21] Cooper ME, Bonnet F, Oldfield M, et al. Mechanism of diabetic vasculopathy: An overview. *American Journal of Hypertension*. 2001;**14**:475-486
- [22] Basta G, Lazzerini G, et al. Advanced glycation end-product activate endothelium signal-transduction receptor RAGE. A mechanism for amplification of inflammatory responses. *Circulation*. 2002;**105**:816-822
- [23] Bucala R, Makita Z, Vega G, et al. Modification of low density lipoprotein by advanced glycation end-products contribute to the dyslipidemia of diabetes and renal insufficiency. Protocol for the National Academy of Sciences USA. *Medical Science*. 1994;**91**:9441-9445
- [24] Okonkwo UA, Di Pietro LA. Diabetes and wound angiogenesis. *International Journal of Molecular Sciences*. 2017;**18**(7):1419
- [25] Dinh T, Veves A. Microcirculation of the diabetic foot. *Current Pharmaceutical Design*. 2005;**11**(18):2301-2309
- [26] Selvin E, Marinopoulos S, Berkenblit G, Rami T, et al. Meta-analysis: Glycosylated hemoglobin and CVD disease in diabetes mellitus. *Annals of Internal Medicine*. 2004;**21**:421-431
- [27] Ayuk SM, Abrahamse H, et al. The role of matrix metalloproteinases in diabetic wound healing in relation to photo bio modulation. *Journal of Diabetes Research*. 2016;**2016**:9. Article ID 289756. Available from: <http://dx.doi.org/10.1155/2016/289756>
- [28] Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *Journal of Clinical Investigation*. 2007;**117**(5):1219-1222
- [29] Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;**50**(1):18-25
- [30] Lipsky BA, Anthony R, et al. Infectious Diseases Society of America clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clinical Infectious Diseases*. 2012;**54**(12):132-173
- [31] Gadepalli R, Dhawan B, Sreenivas V, et al. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. *Diabetes Care*. 2006;**29**:1727-1732
- [32] Wagner FW. The dysvascular foot: A system of diagnosis and treatment. *Foot & Ankle*. 1981;**2**:64-122
- [33] Chuan F et al. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. *PLoS One*. 2015;**10**(4):e0124739
- [34] Armstrong D, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: The contribution of depth, infection and ischemia to risk of amputation. *Diabetes Care*. 1998;**21**(5):855-859
- [35] Terashi H, Kitano I, Tsuji Y. Total management of diabetic foot ulcerations: Kobe classification as a new classification of diabetic foot wounds. *The Keio Journal of Medicine*. 2011;**60**:17-21
- [36] Macfarlane RM, Jeffcoate WJ. Classification of diabetic foot ulcers: SAD system. *The Diabetic Foot*. 1999;**2**(4):123-130
- [37] Game F. Classification of diabetic foot ulcers. *Diabetes/ Metabolism Research and Reviews*. 2015;**32**(1):186-194

- [38] Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. *Diabetologia*. 2002;**45**:1085-1096
- [39] Madan SS, Pai DR. Charcot neuroarthropathy of the foot and ankle. *Orthopaedic Surgery*. 2013;**5**(2):86-93
- [40] Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: A systematic review. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;**25**:1463-1469
- [41] Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes*. 1991;**40**(10):1305-1313
- [42] Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: The Seattle Diabetic Foot Study. *Diabetes Care*. 2006;**29**:1202-1207
- [43] Verity S, Sochocki M, Embil JM, Trepman E. Treatment of Charcot foot and ankle with a prefabricated removable walker brace and custom insole. *Foot and Ankle Surgery*. 2008;**14**:26-31
- [44] Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: A systematic review and metaanalysis. *Diabetes/ Metabolism Research and Reviews*. 2013;**29**:183-193
- [45] Lipsky BA, Aragón-Sánchez J, Diggle M. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. *Diabetes/Metabolism Research and Reviews*. 2016;**32**(1):45-74
- [46] LoGerfo FW, Gibbons GW, Pomposelli FB Jr, Campbell DR, Miller A, et al. Trends in the care of the diabetic foot. Expanded role of arterial reconstruction. *Archives of Surgery*. 1992;**127**(5):617-621. DOI: 10.1001/archsurg.1992.01420050145019
- [47] Albayati MA, Shearman CP. Peripheral arterial disease and bypass surgery in the diabetic lower limb. *The Medical Clinics of North America*. 2013;**97**:821-834
- [48] Schindl A, Schindl M, Schön H, Knobler R, Havelec L, et al. Low intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care*. 1998;**21**:580-584
- [49] Pai DR, Madan SS. Techniques in chronic wound management: Review of the literature and recent concepts. *Journal of Novel Physiotherapies*. 2013;**3**:22-27
- [50] Wong MW, Leung PC, Wong WC. Limb salvage in extensive diabetic foot ulceration—A preliminary clinical study using simple debridement and herbal drinks. *Hong Kong Medical Journal*. 2001;**7**:403-407
- [51] Wu L, Norman G, Dumville JC, et al. Dressings for treating foot ulcers in people with diabetes: An overview of systematic reviews. *Cochrane Database of Systematic Reviews*. 2015;**14**(7):CD101471
- [52] Shukrimi A, Sulaiman AR, Halim AY, Azril A. A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. *The Medical Journal of Malaysia*. 2008;**63**:44-46
- [53] Shaikh IA, Masood N, Shaikh FA, Shaikh MA. Diabetic foot ulcers; correlation of nutritional status of type 2 diabetic patients of Hyderabad Sindh, Pakistan. *The Professional Medical Journal*. 2017;**24**(5):707-712

[54] Younis BB, Shahid A, Arshad R, Khurshid S, Masood J. Charcot osteoarthropathy in type 2 diabetes persons presenting to specialist diabetes clinic at a tertiary care hospital. *BMC Endocrine Disorders*. 2015;**15**:28

[55] Wukich D, Sung W, Wipf S, Armstrong DG. The consequences of complacency: Managing the effects of unrecognized Charcot feet. *Diabetic Medicine*. 2011;**28**(2):195-198

[56] Rogers LC, Frykberg RG. The charcot foot. *Medical Clinics of North America*. 2013;**97**(5):847-856

[57] Saltzman CL, Hagy ML, Zimmerman B, et al. How effective is intensive nonoperative initial treatment of patients with diabetes and Charcot arthropathy of the feet? *Clinical Orthopaedics and Related Research*. 2005;**435**:185-190