Pathophysiology and management of diabetic foot ulcer: Review.

Kedar Prasad Meena*, Tripty Karri, Pradeep Samal, Divya Jaiswal, Sandeep Yadav

Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India

Received: *01-May-2023, Manuscript No. AADY-23-97500;* ***Editor assigned:*** *03-May-2023, AADY-23-97500 (PQ);* ***Reviewed:*** *17-May-2023, QC No. AADY-23-97500;* ***Revised:*** *03-Jul-2023, Manuscript No. AADY-23-97500 (R);* ***Published:*** *10-Jul-2023, DOI:10.35841/aady.7.5.161*

Abstract

Diabetes is a common disease affected by many people throughout the world. The many tissues and organs are affected by long term hyperglycemia. It is optimized by different management approaches and sometimes along with adjuvant therapy. Based on studies advanced dressing, blood sugar control wound debridement and offloading modalities should always be a part of diabetic foot ulcer management. If this is not well controlled by antidiabetic medications, it will in chronic complications including heart disease, stroke, diabetic nephropathy, neuropathy, retinopathy, peripheral arterial disease and diabetic foot with poor wound healing. Diabetic Foot Ulcer (DFU) is one of the costly and devasting long term aggravation of diabetes mellitus, which affects around 15%-20% of diabetic patients during their lifetime. Chronic foot ulcer heals slowly or sometimes not at all. It might show long term hospitalization. The cost of medical care products associated with ulcer healing results in a burden on the healthcare system and variability in etiology observed in foot ulcers. The management of diabetic foot ulcer is a multidisciplinary approach for the management of wound.

Keywords: Diabetes mellitus, Diabetic foot ulcer, Epidemiology, Amputation, Diabetic Neuropathy (DN), Wound management

Abbreviation: DFU: Diabetic Foot Ulcer; DF: Diabetic Mellitus; DN: Diabetic Neuropathy; PAD: Peripheral Arterial Disease

Introduction

Diabetic Foot Ulcer (DFU) is one of the most common complications of diabetes, is a progressive wound occurred on diabetic skin with irregularly delayed wound healing rate due to impaired physiological conditions and weak immune responses [1]. FU is a multifactorial disease that results from lower limb amputation [2]. About 415 million people in the world are diagnosed with DM and the majority of them are due to type 2 DM. It is predicted to increase by 642 million people by the year 2040. In diabetes mellitus person, developing of non-healing foot ulcer is multifactorial disease and this result in to lower limb amputation. These factors are poor epithelialization, persistent inflammatory phase, reduced blood flow and angiogenesis, unbalance level of enzymatic activities and epigenetic changes. DFU is defined as the foot affected by ulceration that is associated with peripheral arterial disease and neuropathy of the lower limb in diabetic patients.

Literature Review

Epidemiology

Diabetic foot is a complication associated with diabetes with reduced quality of life, morbidity, mortality and costs. Diabetic foot presents ulcers, infections, peripheral neuropathy (Charcot foot), and peripheral arterial disease in diabetic patients. For lower extremity amputations it is the most important precursor [3,4].

Global diabetic foot ulcer prevalence was 6.3%, which was higher in males (4.5%) than females (3.5%) and higher in type 2 diabetic patients (6.4%) than type 1 diabetics (5.5%). There is 25% life time risk for developing a foot ulcer in diabetes person.

Diabetic currently affects more than 62 millions Indians, which is more than 7.2% of the adult population. Among them, 6.7% prevalence is young and middle aged adults and 5.6% is prediabetes according to the national family healthy survey-4. The average age on onset is 42.5 years.

Materials and Methods

Etiology of DFU

There are several factors responsible for the diabetic foot ulcer. Some of these are gender (male), diabetes duration time, age of patients, high body mass index, other comorbidities such as retinopathy, diabetic peripheral neuropathy, peripheral vascular disease, glycated Hemoglobin level (HbA1C), foot deformity and higher. Plantar pressure, infections and improper foot care [5]. Most DFUs are caused by neuropathic, ischemic or combined neuroischemic abnormalities. Out of this 90% is caused by neuropathy alone or with ischemia and 10% are caused by pure ischemic. Recent studies have indicated the incidence of neuroischemic problems has increased and neuroischemic ulcers are the most common ulcers seen.

The most common pathway to develop foot problems in diabetes is peripheral sensorimotor and autonomic neuropathy which leads to high foot pressure, foot deformities and gain instability, which increases the risks of developing ulcers [6-8]. Two major factors with various components of diabetic foot ulcer in diabetic patients (Tables 1 and 2).

- **Causative factor:** Peripheral neuropathy, high foot plantar pressure, trauma.
- **Contributive factor:** Atherosclerosis, diabetes.

Causative factors: It shows Table 1.

Table 1. *Causative factors of peripheral neuropathy, high plantar foot pressure and trauma.*

Peripheral neuropathy (sensory, motor, autonomic)	• It is most important causative factor. • In this sensation of pain and pressure are lost and proprioception of the loss of foot position sensation. • Motor neuropathy affects all the muscles in legs, resulting protrusion of abnormal bones, foot normal architecture changed, deformity of foot results such as hammer toe and hallux rigidus. • In this dry skin and less or no sweating is the symptom of autonomic neuropathy/autosimpatectomy and increased secondary capillary refill due to arteriovenous shorts in the skin, skin crust, triggering fissures, all makes the foot vulnerable to minimal trauma.
High plantar foot pressure	• Here limitations of joint mobility and foot deformities observed. Diabetic patients with high plantar foot pressure are high chance of foot ulcer compare to patients without high plantar foot pressure. It is mainly observed in patients with peripheral neuropathy.
Trauma	• It is especially recurring trauma.by footwear friction chances of occurring trauma are 21%, by foot injury it shows 11% chances, while fingernail cut errors 4% and 4% cellulitis due to complications of tinea pedis.

Contributive factors: It shows Table 2.

Table 2. *Contributive factors of atherosclerosis and diabetes.*

Atherosclerosis	• Peripheral vascular disease is responsible for occurrence of this, especially due the blood vessels of femoropopliteal and small blood vessels below the knee. • In diabetic patients' risk of ulcer is high/twice.
Diabetes	• Diabetes itself a factor which affects the wound healing, if it was not controlled properly. • It includes collagen cross linking disorder, metricoproteinase matrix functional disorders and immunologic disorders, like impaired PMN function. • Diabetes has high rate of onychomycosis and tinea infections. • DM characterized by sustains hyperglycemia as well as increased inflammatory mediators, triggers an inflammatory response, leading to chronic inflammation of low grade. • Inflammation and neovascularization are important in wound healing.

Peripheral neuropathy and Peripheral Arterial Disease (PAD) or both pay a central role therefore DFU categorised as neuropathic, neuroischemic, ischaemic [9,10].

Where neuroischaemic is the combined effect of ischemia and neuropathy, where macrovascular disease in some instance, microvascular dysfunction impair perfusion in diabetic foot (Table 3).

Table 3. *Features of DFUs according to etiology.*

Features	**Neuropathic**	**Ischaemic**	**Neuroischeamic**
Sensation	Sensory loss	Painful	Degree of sensory loss
Wound bed	Pink and granulated surrounded by callus	Necrosis commonly occur	Prone to necrosis minimal callus
Foot temperature and pulses	Warm with bounding pulses	Cool with absent pulses	Cool with absent pulses
Typical location	Weight bearing area of foot metatarsal head, heal and dorsum of clawed toes	Lateral borders of toes; tip of toes, nail edge and between the toes	Margin of foot and toes

Results

Pathophysiology of DFU

Diabetic neuropathy and diabetes related vascular disease combined results to DFU. Diabetes person have high risk of endothelial proliferation, atherosclerosis, arterial hyalinosis and most importantly shows vascular basement membrane thickening (capillary structural alternation of small blood vessels in diabetes) [11].

Hyperglycemia (high glucose level) results lose flexibility and abnormally function of cell membrane due to tissue hyperglycemia physiological variations observed. Due to hyperglycemia nerve damage observe by different physiological ways, e.g. on the basis of diameter of nerve; if small diameter nerve present than it shows less myelination so that it being more chance of injured [12-14]. Few mechanisms of nerve damage because of hyperglycemia are:

- Mechanical conduction defect.
- Metabolic effect.
- Compartment compression effect.

With decreased oxygen level, impaired sensory and motor nerve occurs for a long period of time resulting in an environment in which traumatic events occur which results in DFU [15]. The primary reason for DFU is deficiency of oxygen due to microvascular and macrovascular examination. It was found that type 2 DM patients 40% were suffering from neuropathy and the prevalence of diabetic type 1 neuropathy across Europe is 28% [16]. It results from the combined effect of diabetes related vascular disease and neuropathy (Figure 1) [17-20].

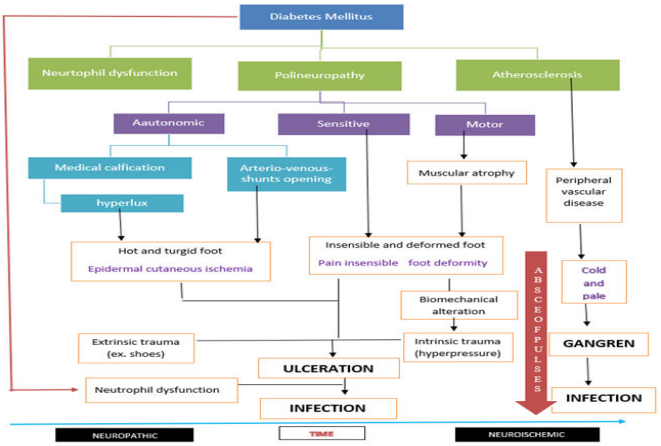

Figure 1. *Pathophysiology of diabetic ulcer: With time neuropathic infection progress toward neuroischemic infection.*

Types of diabetic ulcer

Edmon divided diabetic foot ulcers into two groups namely.

Neuroischemic ulcers: In these colder feet and not detectable beat/pulsation. The skin is observed without hair, thin and smooth, wilt of subcutaneous tissue found.

Neuropathic ulcer: In these feet is warm and pulsation is good (palpable). Perspiration is reduced with dry and cracked skin.

Degree and stages of diabetic ulcer

The university of Texas diabetic ulcer classification system assesses the depth of ulcer penetration and the presence of clinical signs of lower extremity ischemia (Table 4 and Figure 2).

Table 4. *Wagner ulcer classification system.*

Grade/stages	Lesion
0	May have deformity/cellulitis, no open lesion.
1	Superficial ulcer with partial or full thickness.
2	Ulcer extension to ligament, joints, tendon or deep fascia. Without abscess or osteomyelitis.
3	Deep ulcer having abscess or osteomyelitis.
4	local gangrene.
5	Gangrene involvement of entire foot.

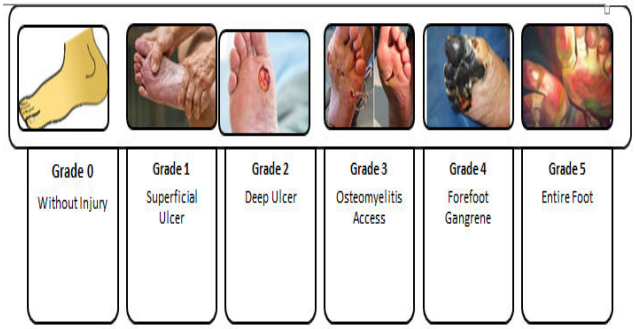

Figure 2. *Grade of foot ulcer: Grade/stage 0 to 3 can be recovered reversibly, at stage 4 it converted to gangrene.*

Clinical diagnosis of DFU

Management of DFU involved rehabilitation the cause of foot ulcer disease, good vulnerology and recurrence of foot ulcer by deep anamnesis and physical examination (Table 5).

Table 5. *Diabetic foot ulcer diagnosis examinations.*

History	Peripheral neuropathy symptoms observed (e.g. radicular pain, hypesthesia and paresthesia). Asymptomatic-Atherosclerotic disease in lower extremity. Pain at rest, non-cured wound, leg pain. Cramps, weakness and discomfort in legs felt due to diabetics (tibioperoneal atherosclerosis)
Physical examination	Ulcer grade examination, analysis of possible peripheral neuropathy and analysis of vascular insufficiency.
Laboratory examination	Measurement of metabolic data such as blood glucose, serum creatinine (determine the adequacy of glucose regulation), renal function. Blood test-leukocytosis count (indication of infection of the foot). If anemia is observed than wound healing slowdown or inhibited. Pulse volume recording examination.
Radiological examination	With the help of Computer Tomographic (CT) and Magnetic Resonance (MRI). A normal examination of the diabetic foot may show demineralization and presence of osteomyelitis. Conventional angiography when vascular or endovascular surgery is planned. To show arteriosclerotic disease arteriography is necessary.

Discussion

Treatment and management of DFU

Wound closure is the prime goal of the treatment of DFU. Its treatment and management are based on stage of ulcer, vascularity and presence of infection. A multibranched approach notably glycemic control, debridement of the wound, revascularization, infection management, off-loading systems and suitable contemporary dressing for treatment of foot ulcers is mandatory along with the other adjunct therapies. There are various treatment manners for DFU as majorly comes as two therapies: Conventional therapy and contemporary adjunct therapy. Under conventional therapy conventional dressing, antimicrobial agents, maggot therapy and offloading come. Where in contemporary adjunct therapy; electric stimulation therapy, hyperbaric therapy, low intensity laser/photosensitive therapy and acellular/cellular dressings with bioactive comes.

In wound dressing polymers and their substitutes are used, either natural polymeric form collagen, gelatin, silk, chitin/chitosan, cellulose, hyaluronic acid and synthetic polymeric forms poly lactic acid, poly-caprolactone, PLGA, polyurethanes.

The probability of regeneration is high when suitable dressing material contained proper biopolymeric scaffolds used. Biomolecules that regulate the protein synthesis and growth factors. These are parameters such as temperature, pH, enzyme concentration, moisture, oxygen, mechanical stability and electrical signals that act as markers for the healing process.

Adjuvent therapy: In diabetic foot ulcer some medications such as herbal treatments, molecular research and oxygen therapy used. In alternative medication treatment includes old traditional herbal treatment to more innovative ultrasonic therapy. Wound healing shows by granulation and angiogenesis results with positive outcome. With better granulation herbal treatment shows fast healing, better surface oxygen tension and microcirculation.

In molecular research by using various growth factors such as granulocyte colony stimulating factors, fibroblast growth factor has established clinical value of their topical application.

Oxygen therapy (hyperbaric oxygen treatment) more used in chronic ulcer and gangrene with success rate of 70%. In diabetic foot, biomaterial technology provides a way to infection control, oxygenation and hydration to wound bed.

Foot ulcer treatment is a multidisciplinary approach, that needed to be employed because of the multifarious responses of diabetic Foot Ulcer (FU) and the numerous diseases or conditions within the patient's body at the same time occurs. This significant improvement includes a reduction in the incidence of major amputation.

The essential component of treatment is rest, relief of pressure and upgrading of the affected foot. It was initiated at first pre-sensation.

On the basis of grade/stages of foot ulcer and frequency of vicinity and non-appearance of ischemia diabetic foot ulcer is performed. Debridement (necropsy), offloading at injured area reduction of pressure, diagnosis of the type of bacteria for management of infection and providing antimicrobial drugs and foot ulcer treatment using wound dressing clean.

Inflammation and infection control: If the person with DFU has a superficial skin infection or mild infection should give oral antibiotic therapy. That will target the beta-hemolytic *Streptococcus* and *Staphylococcus aureus*. The topical antimicrobials either as an adjunctive therapy alone or to systemic therapy work to reduce the bacterial load and prevent the ulcer from further contamination. Early stage treatment prevents further spreading of infection to deeper tissues.

Conclusion

The annual incidence of diabetic foot ulcer will increase in the future and it requires high cost of care. The risk factors for diabetic foot ulcers such as diabetic retinopathy, patients with diabetes are more susceptible to distal lower limb arterial disease; it mainly shows ischemia in affected smaller arteries below the knee and inside the foot. Neuropathy allows ulceration after unrecognized trauma, and ischemia (where poor blood supply) inhibits wound healing. It can cause amputation in the lower extremities. DFU healing also takes a long time. Foot ulcer healing requires primary infection control than inflammatory repair followed by regeneration of connective tissue matrix, vascularization, angiogenesis, re-epithelization and constriction of wound.

The administration of foot ulcer therapy is debridement/ necropsy, managing the infection and reducing offloading. Ulcer treatment providing primary by using wound dressing clean and moist and by detecting the type of bacteria adequate antibiotics provide to reduce/manage infection.

References

1. Rastogi A, Ghanshym G, Kesavan R, et al. Long term outcomes after incident diabetic foot ulcer: Multicenter large cohort prospective study (EDI-FOCUS investigators) epidemiology of diabetic foot complications study. Diabetes Res Clin Pract. 2020;162:108113.
2. Monterio SM, Boyko EJ, Jeffcoat W, et al. Diabetic foot ulcer classifications: A critical review. Diabetes Metab Res Rev. 2020;36(S1):3272.
3. Izadi M, Kheirjou R, Mohammadpour R, et al. Efficacy of comprehensive ozone therapy in diabetic foot ulcer healing. Diabetes Metab Syndr. 2019;13(1):822-5.
4. Chanda A, Unnikrishnan V. Novel insole design for diabetic foot ulcer management. J Eng Med. 2018;232(12): 1182-95.
5. Netten VJ, Woodburn J, Bus SA. The future of prevention of diabetic foot ulcer: A paradigm shift from stratified healthcare towards personalized medicine. Diabetes Metab Res Rev. 2020;36 (Suppl 1):e3234.
6. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes 2015;6(1):37-53.
7. Holden P, Nair LS. Deferoxamine: An angiogenic and antioxidant molecule for tissue regeneration. Tissue Eng Part B Rev. 2019;25(6):461-70.
8. Frykberg RG. Diabetic foot ulcers: Pathogenesis and management. Am Fam Physician. 2002;66(9):1655-62.
9. Hou Z, Nie C, Si Z, et al. Deferoxamine enhances neovascularization and accelerates wound healing diabetic rats *via* the accumulation of hypoxia inducible factor-1α. Diabetes Res Clin Pract. 2013;101(1):62-71.
10. Lavery L, Armstrong DG, Wunderlich RP, et al. Risk factors for foot infections in individuals with diabetes. Diabetes Care. 2006;29(6):1288-93.
11. Farahani M, Shafiee A. Wound healing: From passive to smart dressings. Adv Healthc Mater. 2021;10(16):2100477.
12. Dubsky M, Jirkovsk A, Bem R, et al. Risk factors for recurrence of diabetic foot ulcers: Prospective follow-up analysis of a Eurodiale subgroup. Int Wound J. 2013;10(5): 555-61.
13. Lee KM, Kim WH, Lee JH, et al. Risk factors of treatment failure in diabetic foot ulcer patients. Arch Plastic Surg. 2013;40(2):123-8.
14. Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic neuropathy and its relation to glycaemic control and potential risk factors: The EURODIAB IDDM complications study. Diabetologia. 1996;39(11):1377-84.
15. Andrews KL, Houdek MT, Kiemele LJ. Wound management of chronic diabetic foot ulcers: From the basics to regenerative medicine. Prosthet Orthot Int. 2015;39(1):29-39.
16. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018;1411(1): 153-65.
17. Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes Ther. 2012;3(1):4.
18. Roy S, Ha J, Trudeau K, ET AL. Vascular basement membrane thickening in diabetic retinopathy. Curr Eye Res. 2010;35(12):1045-56.
19. Castellano LE, Delgado J, Gonzalez AV, ET AL. Diabetic wound healing with engineered biomaterials. Biomater Organ Tissue Regen. 2020;335-61.

20. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part II. Management. J Am Acad Dermatol. 2014;70(1):21.

***Correspondence to**

Kedar Prasad Meena

Department of Pharmacy,

Guru Ghasidas Vishwavidyalaya (A Central University),
Bilaspur,
Chhattisgarh,
India
E-mail: *meenapharmaceutics@rediffmail.com*