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ORIGINAL ARTICLE

Diabetic Foot Ulcers: Insights into Management and Prevention

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ABSTRACT

Diabetic foot ulcer (DFU) is one of the greatest thoughtful difficulties of diabetes, negatively affecting the patient's health and socioeconomic status. Around the world, diabetes prevalence is increasing in both developing and developed countries. There are several measures in place in most countries to limit diabetes complications. This review summarizes the pathogenic mechanisms that lead to diabetic foot and focuses on prevention and management. It may be possible to prevent diabetic foot ulcers and thus amputation risk by increasing physicians' awareness and ability to identify risky feet. Diabetes neuropathy, peripheral artery disease, and immune dysfunction are the three major contributing factors. In order to treat diabetic foot disease, a detailed history and physical examination are necessary. Diabetic neuropathy and peripheral arterial disease manifestations, such as diabetic foot ulcers and infections, should be examined during this examination. Prevention approaches should integrate a multidisciplinary method centered on patient education. Preventive efforts must, however, be sustained for a long time for them to be effective.

Keywords: Diabetic foot; Ulceration; Neuropathy; Pathogenesis; Peripheral arterial disease

INTRODUCTION

It is a growing problem in the diabetic community to suffer from diabetic foot ulcers. There is alarming concern among medical professionals about the rapid increase in diabetes, a serious lifelong disease. In recent years, it has estimated that 20.8% of the United States (US) population has diabetes problems. Diabetes mellitus persons can develop foot ulcers, ranging from 4% to 10% (Driver and Blume, 2014; Bus, 2012). The infection of diabetic foot ulcers is primary sources of hospital admissions in diabetics (Wu et al., 2007; Nain et al., 2011). DFU has a high mortality as well as morbidity rate (Mayfield et al., 2004; Reiber et al. 1995) regardless of a multidisciplinary methods. Infection of DFU is common (Iraj et al., 2013). The healing time of these ulcers is longer and amputation is more likely to result (Del Core et al. 2018). Diabetes foot management, therefore, is dependent on determining the presence of infection (Uzun et al., 2007; Noor et al., 2017).

Causes and types of FU: It is observe that Ill-fitting shoes are the most important and common cause of ulceration. Researchers have discussed many type of ulcers, but among them, the most common types of ulcers are ischaemic, neuro-ischaemic, and neuropathic. These ulcers are mainly caused by bacteria.

Site and depth, Signs of infection: Neuropathic, neuro-ischaemic, and Ischaemic ulcers frequently arise on the plantar superficial of the tips of toes, foot, and the lateral border of the foot. It is very difficult to determine the depth of ulcers.

Risk Factors: The quality of life can impair due to diabetic foot, demanding continued hospitalization, and having high prices. Diabetic disease accounts for 15% of diabetic foot-related problems, and diabetics who are uncontrolled are 15 times more likely to undergo amputations than their non-diabetic counterparts (Al-Bakri et al., 2021). The study found most patients to be male, probably because they have been exposed to the outside environment and have experienced trauma more often. Multicenter studies conducted in Germany, India, and Tanzania found that all 613 of the patients had neuropathy. Among our patients, 51% had a sensory loss. Studies conducted nationally and internationally have revealed wide variations in the prevalence of sensory neuropathy among diabetic foot ulcer patients. The prevalence of this condition is 20-40%10, but Ali et al. (2008) found that it occurred in 44% of their patients.

An amputation or a nonhealing ulcer caused by poorly controlled blood glucose levels had a direct impact on the disease's outcome. Germany had a 48% risk of foot ulcers due to PAD, whereas India and Tanzania had a 12% and 13% risk, respectively. Infection was observed in 85.7% of our patients, which is consistent with an Indian study (Viswanathan, 2010). Diabetic patients were most likely to develop foot ulcers from pressure from their footwear. Similar risk factors have been reported by Ahmad et al. (2013) from Pakistan.

An experimental research or study was performed in Kenya in 2003 to conclude the risk factors for DFU (Nyamu et al., 2003). They investigated that diabetes peoples for a long period of time are more likely to grow DFU. There was a prevalence of neuroischaemic (30.5%), neuropathic (47.5%), and ischaemic (18%) ulcers. A significant difference in glycaemic control was observed for neuropathic ulcers related to further types, as well as the elongated interval (23.3 weeks). There was a significant increase in total cholesterol and diastolic blood pressure among patients with ischemic ulcers compared to other ulcer types. The most common type of Wagner ulcer was stage 2 (49.4%), but stage 4 ulcers were the best scorer (7.8/10) and lasted the longest (23.6 weeks). The ulcers contained 73.2% of aerobic pathogens.

Organisms isolated from ulcer: Several bacterial isolates have been isolated from diabetic foot ulcer patients. Different techniques and taxonomic identification keys have been used to isolate and identify these isolates. According to the findings of Girish et al. (2010), Al Benwan et al. (2012), and Hadadi et al. (2014), Gram-negative bacteria are the main causative agents of diabetic foot infections. Most organisms isolated were pseudomonas and klebsiella. Multi-drug resistance was high in Pseudomonas. The treatment of ulcers should be based on the sensitivity of the infection in order to reduce multidrug resistance. Organisms secluded from DFU are given in table 1.

Table 1: Organisms secluded from DFU patients.

Isolates	Country	References
Staphylococcus aureus	Africa	Sotto et al., 2008
Streptococcus agalactiae	Saudi Arabia	Alkhatieb et al. 2022
Enterococcus avium	Saudi Arabia, India	Alkhatieb et al. 2022; Zubair et al. 2010
Staphylococcus epidermidis	Saudi Arabia, India	Zubair et al. 2010; Alkhatieb et al. 2022
Escherichia coli	Saudi Arabia	Alkhatieb et al. 2022
Klebsiella pneumoniae	Saudi Arabia, Bangalore	Alkhatieb et al. 2022; Mukkunnath et al., 2015
Pseudomonas aeruginosa	Saudi Arabia	Alkhatieb et al. 2022
Proteus vulgaris	Saudi Arabia	Alkhatieb et al. 2022
Proteus mirabilis	Saudi Arabia, India	Alkhatieb et al. 2022; Zubair et al. 2010
Citrobacter freundii	Saudi Arabia	Alkhatieb et al. 2022
Serratia marches	Saudi Arabia, Ethiopia	Alkhatieb et al. 2022
Aeromonas hydrophilic	Saudi Arabia, Bangalore	Alkhatieb et al. 2022; Mukkunnath et al., 2015

Morganella morganii	Saudi Arabia	Alkhatieb et al. 2022
Acinetobacter baumannii	Saudi Arabia	Alkhatieb et al. 2022
Enterococcus faecalis	Saudi Arabia, Egypt	Alkhatieb et al. 2022; Nabiel and Barakat, 2017
Candida albicans	Egypt, India	Aldhfyan et al. 2018; Zubair et al. 2010
Enterococcus avium	Egypt, Bangalore	Aldhfyan et al. 2018; Mukkunnath et al., 2015
Streptococcus pyogenes	Bangalore	Mukkunnath et al., 2015
Clostridium perfringens	India	Garg et al. 2014; Haldar et al. 2017

Factors affecting the DFU: Patients with foot ulcers, as well as patients with chronic conditions, should take into account and assess all the above-mentioned factors as well as disease-related factors as shown in figure 1 (Crews et al., 2009; Bus et al., 2011). All these features are very significant to determine the diabetic foot ulcer in patients as investigated by many researchers in the world (Al Kafrawy et al., 2014).

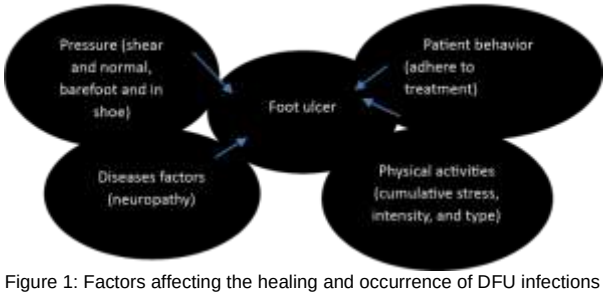

Figure 1: Factors affecting the healing and occurrence of DFU infections

Table 2: Factors to be measured for antibiotic medicament in diabetic foot contagion (Lipsky, 2004; Richard et al., 2011)

Criteria	Comments
Renal dysfunction	Avoid hepatotoxic agents
Poor therapeutic compliance	Ⅳ route and/or hospitalization
Severity of infection	Broad-spectrum therapy via parenteral route for severe infection
Hepatic dysfunction	Avoid nephrotoxic agents
Impaired gastrointestinal function (gastroparesis)	Favor parenteral route
History of new antibiotic handling	May need an extended coverage against Enterococcus and gram-negative bacilli
Chronicity of the wound	Give penchant to broad-spectrum therapy initially
Drug allergies	Review the patient's medical history carefully
Local antibiotic resistance patterns	Cover MRSA if indicated

Pathophysiology and Pathogenesis: Diabetic foot disease has a multifactorial etiology that comprises vasculopathy, immunopathy, diabetic neuropathy, and poor glycemic control. Among these, diabetic neuropathy is the common most cause of DFU and causes motor, sensory, and autonomic nerve dysfunction. With proper screening, neuropathy can be detected in 75% of diabetic patients undergoing ankle and foot surgery (Wukich et al., 2015). In the diabetic population, PAD is frequently observed in conjunction that can contribute in foot complications. 50% of diabetic foot disease patients have some degree of PAD (Suder and Wukich, 2012). Furthermore, diabetes patients have a reduced capacity to support a seditious reaction to contagion (immunopathy). Diabetes patients have impaired chemotaxis, neutrophil function, phagocytosis, and a decreased t-cell response when compared to those who do not have diabetes (Richard et al., 2017).

As reported by many workers that the main risk factors for foot ulceration are PAD, foot trauma, and diabetic neuropathy. Diabetes patients are more likely to suffer from PAD because it begins at a younger age, grows faster, and is generally more prevalent. Ankle and knee areas are usually affected. Researchers have demonstrated that it can predict foot ulceration outcomes as well as cardiovascular disease risks. People with peripheral diabetic neuropathy often experience repetitive minor injuries to their feet that go undetected at the time due to reduced sensation in the feet (calluses, nails, foot deformities) or external causes (shoes, burns, foreign bodies). Especially in patients with peripheral arterial disease, this may lead to ulcer infection and foot amputation.

The most common cause of osteomyelitis is an infection of deep soft tissues that burst through the cortex and into the bone marrow. Almost all foot infections that last for a long time are caused by osteomyelitis. Diagnosing osteomyelitis in diabetic patients is often difficult. Differentiating infections from non-infectious conditions is one of the most challenging things to do, as well as differentiating soft tissue infections from bone infections.

Classification of diabetic foot: Diabetic feet are categories into two groups such as the Neuropathic Foot and Neuroischemic Foot. The system for classifying wounds is given in table 3.

Table 3: System for classifying wounds (Oyibo et al., 2001)

Stages	Description
A	No infection/ischemia
B	Infection present
C	Ischemia present
D	Both (Ischemia and infection) are present
Grading	
0	Epithelialized wound
1	Superficial wound
2	Wound penetrates to tendon or capsule
3	The wound penetrates to bones and joints

Prevention and management: There are three methods of prevention (Pendsey and Abbas, 2007) such as primary, secondary and tertiary. It also consists of the following measures. Modification in lifestyle, control of blood pressure and glycemic, Smoking cessation, and lipid management.

Offloading: The risk of ulceration increases with increased plantar foot pressure, but a pressure threshold above which ulceration commences or below which it heals has not yet been established. Among high-risk diabetic patients at high risk for foot ulceration, barefoot dynamic peak plantar pressure of 700 kPa showed 70% sensitivity and 65% specificity. According to another study, barefoot peak pressures of 875 kPa are 64% sensitive to foot ulcers and 46% specific to them (Armstrong et al., 1998). Patients develop foot ulcers when they have lower than threshold pressures while they don't have such disease when they have higher than threshold pressures. As a result, clinical outcomes cannot be accurately predicted based on barefoot peak pressure measured at the ankle (Lavery et al., 2003).

Role of education in prevention of diabetic foot ulcers in patients: Education is an important step in preventing problems of DFU. Educating patients and caregivers should be the primary focus, but professionals must also become educated so they recognize the nature of patient instructions. Patients and caregivers can benefit from their training and education once they are trained and educated. Patients and caregivers should receive education, as well as professionals, so that patients and caregivers can be efficiently educated. Educated patients are taught how to manage diabetes mellitus, how to care for the foot, and how to use appropriate footwear. Foot hygiene is also a problem among patients. To provide education and screening on a national scale, however, sustained and continuous government intervention is required (Nather et al., 2018; Uzun et al., 2007; Dorresteijn et al., 2012). It has been reported that after six months of education, clinical parameters such as blood pressure, weight, and body

mass index showed a statistically significant positive change in patients (Nemcová and Hlinková, 2014).

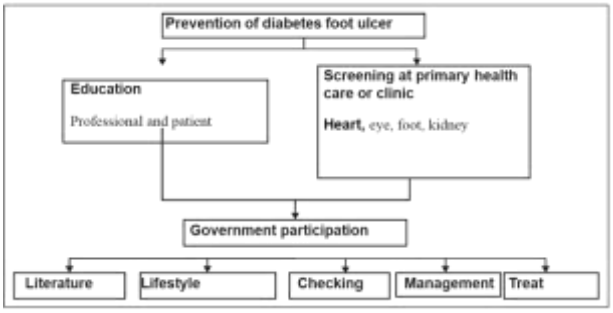

Figure 2: Algorithm for prevention of diabetic foot ulcer (Nather et al., 2018).

Restoration of skin perfusion: The best key factor manipulating the outcome of a diabetic foot ulcer is a peripheral arterial disease. If a diabetic patient has symptoms or signs of ischemia, an ankle brachial pressure index of 0.6, pressures of 50 mmHg, or TcPo2 of 30 mmHg, healing will be severely hampered (Bakker et al., 2012; Noor et al., 2017).

Treatment of infection: Treatment of infection is very important. Clean the necrotic tissues and debris surrounding the callus properly. Empiric oral antibiotic therapy should be started which targeted streptococci and S. aureus (Bakker et al., 2012; Noor et al., 2017). Foot ulcer infections are shown in figure 3.

Figure 3: Infection of foot ulcer on feet of patients (Del Core et al., 2018).

Wound care: Wound inspection and frequent wound debridement. Maintain the moist environment and negative pressure therapy can used (Bakker et al., 2012; Noor et al., 2017).

Keystones of foot management: Five different keystones for food management have been reported like inspection of feet on a daily basis. Education of family, health care, and patient, wearing footwear, and treatment of nonulcerative pathology. These are the keystones that need to be maintained throughout life to prevent infections. Sensory loss can be managed by using the following techniques such as vibration perception, pressure perception, reflexes, discrimination, and tactile sensation (Bakker et al., 2012; Noor et al., 2017).

Dressings and growth factors: It has observed that ulcers heal very fastly under moist conditions and are less likely to become infected. The exudate from a wound contains a high concentration of platelets, cytokines, white blood cells, matrix metalloproteinase (MMPs), growth factors, and many other enzymes. The healing process can promote with the keratinocyte proliferation, angiogenesis, and fibroblast whereas leukocytes and bacterial toxins stop the healing process which ultimately increase the healing period. All this can be done by the use of fibroblast as gel with weekly debridement (Wieman et al., 1998). Initial studies conducted by many researchers in the world (Yang et al., 2011; Uccioli et al., 2011) found becaplermin to have an important and optimistic influence on ulcer healing but many new studies reported negative impacts of high doses of becaplermin on cancers patients (Papanas and Maltezos, 2010; Steed, 1995; Moustafa et al., 2004; de Lalla et al., 2001).

Revascularization: Patients with apparent peripheral ischemia necessitate revascularization because the suitable arterial plasma resource is mandatory for wound curing and the determination of the underlying infection while surgical bypass is a method to treat the ischemic limbs (Pendsey, 2010; **F**aries et al., 2004; Shah et al., 1995).

Extracellular Matrix Proteins: A semisynthetic hyaluronic acid ester, Hyaff (Fidia Farmaceutici, Abano Terme, Italy) is used to promote movement, fibroblast growth, and regulate hydration in patients. According to Yo¨nem et al. (2001), fibroblast is effective, and safe as adjunctive therapy in the ulcers treatment.

Hyperbaric Oxygen: Fibroblasts, endothelial cells, and keratinocytes reproduce more quickly in an oxygen-rich conditions (Veves et al., 2002; Broussard, 2004). By the applications of oxygen, body cells especially leukocytes kill bacteria more quickly and effectively than other cells. The lower cell turnover has reported due to fibroblasts from diabetic individuals than non-diabetic individuals. The administering high concentrations of oxygen could hasten wound healing in diabetics (Shahi, et al., 2012). It is resulted that hyperbaric oxygen therapy improves resulting in increased vascular reactivity, vascular function by modulating mechanisms of vascular responses to various dilator, constrictor agonists in cerebral resistance vessels. The production of vasoconstrictors, vasodilators as well as the sensitivity of vessels to these factors influenced by the therapy.

Negative-Pressure Wound Therapy: The negative-pressure wound therapy (NPWT) is newly launched technique for the treatment of DFU. To keep a sealed environment, recurrent or continuous sub atmospheric pressure is pragmatic via a special pump linked to a strong open-celled foam surface dressing covered with an adhesive drape (Yazdanpanah et al., 2018).

Why diabetic foot ulcer prevention is difficult?: The main reasons for it are: Diabetic patients have no sense and have peripheral neuropathy, high pressure, deformity, and even patient behavior. Patients do not visit the hospital or specialized health care. They take medicine irregularly. They can't wear footwear strongly.

CONCLUSION

Diabetic foot ulcers are expensive, debilitating diseases that have serious consequences for diabetics. All diabetes patients must be trained carefully and thoroughly in preventive measures and foot care. By using different ways such as sympathetic DF, appropriate foot examination, soundings for categorizing foot ulcers, and appropriate management systems with a team approach could use to the limb salvage and prevention of limb amputation for people with diabetes. There is an urgent need to review policies and treatments to achieve goals and lessen the burden of care effectively and efficiently. DFU management remains a main therapeutic challenge. In order to reduce the associated high mortality and morbidity rates, as well as amputation risks, DFU prevention is crucial.

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