EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 12
190-197
Year: 2019

A REVIEW ON MANAGEMENT OF DIABETIC FOOT ULCER

Monika Chowdary Vemineni*

Jagans Institute of Pharmaceutical Sciences, Jangalakandriga(V), Muthukur(M), SPSR Nellore(Dt), Andrapradesh, India.

***Corresponding Author: Monika Chowdary Vemineni**
Jagans Institute of Pharmaceutical Sciences, Jangalakandriga(V), Muthukur(M), SPSR Nellore(Dt), Andrapradesh, India.

Article Received on 02/09/2019 **Article Revised on 23/09/2019** **Article Accepted on 13/10/2019**

ABSTRACT
Ulceration of the foot in diabetes is most common and disabling frequently leads to amputation of the leg. Mortality is high and healed ulcers often reoccur. The pathogenesis of diabetic foot ulceration is complex. Management of diabetic foot ulcer (DFU) requires early expert assessment. Despite treatment, ulcers readily become chronic wounds. There were two kinds of assessment used in diabetic foot ulcer which are risk assessment and wound assessment. The treatments that frequently used in diabetic foot ulcer are systemic treatment and local treatment. Diabetic foot ulcers have been neglected in health care research system, clinical practice is based more on opinion than the scientific fact. Foot problems in diabetic patients remain a major public health issue and are the most common reason for hospitalization of a diabetic patient. A foot complication is severe enough to require hospitalization. Hence, the pathological processes are poorly understood and poorly taught and communication between the many specialties involved is disjointed and insensitive. In this review, the epidemiology, pathogenesis, treatment, management, and assessment of diabetic foot ulcers are described.

KEYWORDS: Amputation, diabetic foot ulcer, management, assessment, hospitalization, treatment.

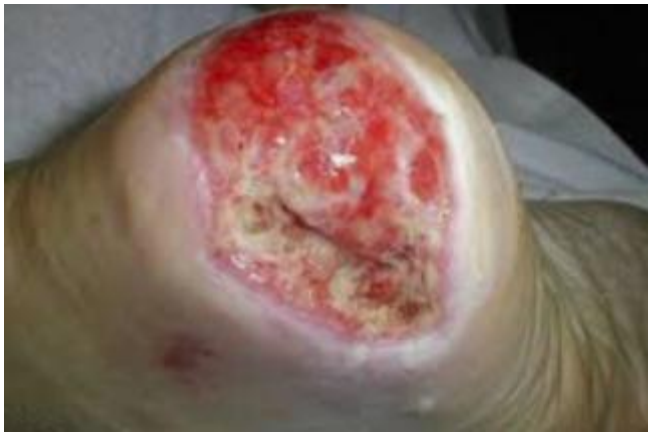
INRODUCTION

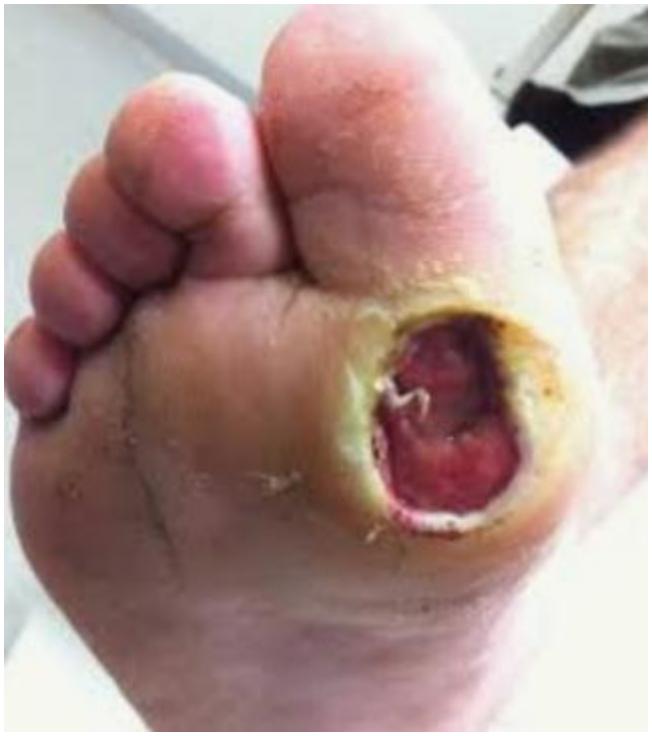
Neuropathy, a serious complication of diabetes, can lead to Charcot changes in the foot. These disrupt the joint stability and the architecture of the foot. There is increased pressure under the sole of the foot with prominence of the metatarsal heads. This leads to ulceration. There is progression from superficial infection to deep and then abscess formation and osteomyelitis.

Ulceration, infection, and gangrene of foot are the leading causes of hospitalisation in patients with diabetes mellitus.[1] Diabetic foot ulcers are a complex problem that leads to foot infection, necrosis and most of the time results in major amputation. Other most common complications include boil, carbuncle, necrotizing fasciitis and gangrene of the foot. Approximately 3–4% of individuals with diabetes have foot ulcers or deep infections and 15% develop foot ulcers during their lifetime. The risk of lower extremity amputation increases by a factor of 8 once an ulcer develops. At 2 years following transtibial amputation, mortality rate is 36%. Figure-1 shows a diabetic foot with spreading gangrene and cellulites.

Although infection is rarely implicated in etiology of diabetic foot ulcers, the ulcers are susceptible to infection once the wound is present. Many of the risk factors for foot ulcer are also predisposing factors for amputation, because ulcers are primary cause leading to amputation.[2]

The emergence of DFU is the result of peripheral neuropathy, ischemia, and neuro-ischemia. Loss of protective sensation and loss of coordination of feet muscle due to neuropathy impacts mechanical stresses during ambulation (Davies, Brophy, Williams, & Taylor, 2006). In addition, decreased oxygen supply in lower limb creates ischemia and it also can cause an actual wound. DFU can be caused by the combination of ischemia and neuropathy which worsen patient's skin integrity. DFU is a complication of DM that can be healed.[3]





ETIOLOGY

The etiology for diabetic foot ulcer is multi factorial .The common underlying causes are poor glycemic control calluses, foot deformities, improper foot care, ill-fitting footwear, underlying peripheral neuropathy and poor circulation, dry skin, etc.[4]

RISK FACTORS

- Peripheral neuropathy (sensory, motor, autonomic)
- Foot deformity (hammer toe, bunion, Charcot, etc)
- Trauma
- Improperly fitted shoes
- Peripheral arterial disease
- Callus
- History of prior ulcers/amputations
- High plantar foot pressures
- Limited joint mobility (cheiroarthropathy)
- Uncontrolled hyperglycemia
- Chronic renal insufficiency
- Diabetes duration
- Blindness/partial sight
- Older age
- Poor knowledge of diabetes.[5]

EPIDEMIOLOGY

The lifetime risk that a diabetic patient will acquire foot lesions (ulcers/gangrene) has been estimated at 15% to 25%, with an annual incidence of 1.0% to 4.1%.[6] The incidence of these lesions appears similar in type 1 vs type 2 diabetic patients, although type 2 diabetic patients comprise approximately 90% of the total diabetic population. In_15% of these patients, ulcers will ultimately lead to amputation.[7]

The risk for an initial foot ulcer is increased in patients who have had diabetes for 10 years, are male, have poor glycemic control, and already have other cardiovascular, renal, or retinal comorbidities.[8] Foot ulcers occur in different rates in different parts of the world and rates of amputations differ as well, with the highest in Native

Americans and lowest in Madrid, Spain. Specifically in North America, foot ulcers and amputations are more common in ethnic minority groups, especially Hispanics and African Americans, as well as in other groups of patients who lack health insurance. As the number of newly diagnosed diabetics is increasing nearly, the incidence of diabetic foot ulcer is also bound to increase.[9] As the number of newly diagnosed diabetics is increasing nearly, the incidence of diabetic foot ulcer is also bound to increase.[10]

PATHOGENESIS

Ischemia, neuropathy, and infection are the three pathologic components that lead to diabetic foot complications, and they frequently occur together as an etiologic triad. The most important principle in treating foot ischemia in patients with diabetes is recognition that the etiology of this ischemia is macro-vascular occlusion of the leg arteries due to atherosclerosis. For many decades, clinicians mistakenly ascribed to the theory of "small vessel disease," or micro-vascular occlusion of arterioles, as the cause of ischemic complications. This theory directly caused the widespread erroneous opinion that patients with diabetes and ulcers would absolutely need amputations because revascularization was not possible. The idea originated from a single histologic study of amputated limbs from diabetic patients, whereby a material positive for periodic acid Schiff occluded the arterioles. A subsequent prospective study[11] of amputation specimens however, refuted the notion of an arteriolar occlusive lesion associated with diabetes. It is now well-recognized that diabetic patients typically have tibial and peroneal arterial occlusive disease with relative sparing of the foot arteries, and ischemia results from atherosclerotic macro-vascular disease as well as from microcirculatory dysfunction.[12]

Diabetic neuropathy has multiple manifestations in the foot because it encompasses sensory, motor, and autonomic fibers. The pathogenesis of diabetic neuropathy is not fully understood. Possible explanations are based on theories of alterations in the vaso nervorum or abnormalities in metabolism. The vascular theory relates to thickening of the nutrient vessels that may occlude with progression, resulting in ischemic injury to the nerve. A more popular theory is the increased activity of the polyol (sorbitol) pathway.[13] Accumulation of sorbitol has been shown in aortic intima and media. Excess sorbitol may produce toxic effects, resulting in demyelination and impaired velocity of peripheral nerve conduction. These pathologic findings have been reported in human diabetic neuropathy.[14] Sensory neuropathy affects the small-diameter pain and temperature fibers first, and susceptibility to injury is increased because these patients are less sensitive to pressure-related trauma or other minor skin injuries. Motor neuropathy affects the longer fibers that innervate the foot, affecting both the intrinsic foot muscles and leg muscles. Autonomic neuropathy causes dry skin through the loss of sweat and oil gland function.

MANAGEMENT OF DIABETIC FOOT ULCER

Diabetic foot ulcers have a high number of morbidity and until today they are still complex to manage. DFU have rapid progress and they can develop many complications that can threaten life and limb (Bentley & Foster, 2008). It should take a proper assessment and management to reduce further impacts of this disease. Management in DFU consists of assessment and treatment. It covers both general conditions and site of ulcers. General assessment in patients with diabetes includes diabetes status, previous history of DFU, previous amputation, risk factor of DFU, symptoms of peripheral arterial disease and medication used (Harries & Harding, 2015). Moreover, treatments in DFU consist of general treatment for diabetes status and in the site of wound.

Appropriate management in site ulceration and systemic body metabolism become an important thing while treating DFU. Strategies to increase wound healing and prevent recurrence of DFU should be stressed on good glycemic, foot care, diet and exercise (Vileikyte, 2001). DFU has become a serious problem in world-wide and its management needs a multi-disciplinary approach. This review purposes to present current evidence-based assessment, treatment strategies of DFU and this review may be useful for nurse who involved in overall management of diabetic foot ulcer.[15]

ASSESSMENT

Nowadays, the number of complication in diabetes involving DFU is high. However general practitioners tend to ignore assess diabetic patient regarding its complication. Less than 50% of diabetic patients reported that they received proper assessment according to DFU (Bowering, 2001). Based on literature there are two kinds of assessment for DFU: risk assessment and wound assessment.[15]

1. RISK ASSESSMENT

Several assessment tools have been developed to measure risk factor of DFU regarding neuropathy.

a. Neuropathic assessment

Several articles mentioned that Neuropathy Symptom Score (NSS) has proven valid and sensitive tool to assess neuropathy (Asad, et al, 2009; Alexiadou & Doupis, 2012). NSS tool assess foot according to sensation, whether both feet can determine burn, tingling, pain and locate its location. It consists of seventeen items which focus on sensory disturbances, muscle weakness, and autonomic symptoms. However, NSS reported was too complex to apply in daily general practices. One comparative study tries to compare effectiveness NNS with Diabetic Neuropathy Symptoms (DNS). DNS consists of some following items which is simpler. DNS score each item from 0 which represents absence of neuropathy symptoms to maximum score 4 points which represent severe neuropathy. This tool assesses about (1) walking ability, (2) pain sensation or arching on feet, (3)

prickling sensations, and (4) numbness in legs or feet (Meijer, et al., 2002).

Although NSS was widely used and proven, DNS also showed a significant correlation (Spearman r) with NSS. Therefore, DNS also has high sensitivity and specificity for evaluating neuropathy (Meijer, et al., 2002).

b. Circulatory assessment

Doppler ultra-sonography can be used to measure Ankle Brachial Index (ABI) and it is widely used to determine blood flow of peripheral artery. However, ABI might result in false positive in diabetic patients, especially in diabetic patient because artificial high systolic pressure of ankle in diabetic patient is common due to calcification of the media distal arteries and it causes vessel relatively incompressible. However, the use of ABI with Doppler ultra-sonography could use for early detection and it might reduce limb complications (Ikem, Ikem, Adebayo, & Soyoye, 2010).[15]

2. WOUND ASSESSMENT

General practitioners including nurses have to monitor DFU progress to evaluate whether specific intervention is effective or is not. Some tools developed to measure wound healing in DFU. PUSH tool (Pressure Ulcer Scale for Healing). PUSH tool which developed by (NPUAP) National Pressure Ulcer Advisory Panel actually creates in purpose to monitor progress of wound healing in pressure ulcer. Nowadays this tool has been validated and used for monitoring pressure ulcer as well as venous ulcer healing. However, current prospective study tries to use PUSH tool to monitor DFU (Gardner, Hillis, & Frantz, 2011).

PUSH tool consists of three domains: length x width, exudate amount, and tissue type. Length x, width, centimeter ruler used to measure length and width (side to side). This tool also measures pus quantity with none, light, mode-rate, or heavy during wound dressing. Gardner, et al. (2011) examined whether PUSH tool valid or not to predict healing in DFU. The result showed PUSH tool score of 10 would be expected wound to be healed in 8.8 weeks and PUSH score of 4 in 2.6 weeks.

The wound's Size (Area and Depth), Sepsis, Arteriopathy, and Denervation [SAD] of DFU description. However, some author's mention this tool shows non-regular in structure so it makes harder to remember (Abbas, et al., 2008). Wegner score**.** The purpose of Wagner system is to assess the depth of ulcer and the presence of gangrene or osteomyelitis. This tool consist of 0-5 linear grading (grade 0 (pre-or post-ulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene). Wagner is the most frequent tool to measure the development of the wound because this tool is easy to apply and reliable. One study showed positive trend of Wegner score to predict increased number of amputation. Wegner score can be used as a tool to monitor wound development (Karthikesalingam, et al., 2010).

University of Texas wound classification systems (UT system). The purpose of UT system is to measures the depth of ulcer, presence of wound infection, and presence of symptoms of lower-extremity ischemia. UT system consists of 0–3 linear grading. Grade 0 pre or post-ulcerative that healed, grade 1 only showed superficial ulcer, grade 2 ulcer penetrate to tendon and grade 3 ulcer penetrate to bone and joint. Moreover there are four stages within each wound grade: stage A is cleans wound, stage B is infected wounds but still non-ischemic, stage C is already developed ischemic but wounds still non-infected, stage D is infected and ischemic wounds.[15]

TREATMENT

1. Systemic Treatment

The important treatment of patients with DFU is to control diabetes systematically. Nutritional management and blood sugar control are very influential for the patient's recovery.

a. Blood Sugar Control

Historically, inadequate blood sugar control can induce foot ulcer due to limb neuropathy. Currently, no studies developed in human to determine whether blood sugar control have benefit for foot ulcer. How-ever, studies in animal showed hyperglycemia impairs wound healing. So, keeps blood sugar in reasonable level can improve healing.[15]

b. Nutrition to Promote Wound Healing

Chronic wound needs a lot of resources in daily routines to promote wound healing including nutritional support. Nutritional support is essential in DFU; it is due to during wound healing process tissue demand more energy. Energy and protein usually become main resources for building a new cell. Therefore, undernourished and malnourished patients can be very challenging to take concern (Wild, et al., 2010). Patients is unique and different with each other, therefore clinical significant of nutrition and wound healing also individually different. However, general practitioners must decide what, when and how nutritional supplementation needs. A systematic review by Wild et al (2010) described macro and micronutrients that can improve wound healing.

There are 5 main nutrients which can improve wound healing: (1) protein supply is necessary because it relate with synthesis collagen the production of fibroblast, (2) fatty acids are substrate of eicosanoid synthesis and one of cell membranes components which promotes inflammatory phase, (3) vitamin C is important for optimizing immune response, cell mitosis and monocyte migration to wound tissue that changed into macrophages during inflammatory process, (4) zinc

becomes cofactor for some enzyme and it is involved RNA, DNA and proteins synthesis, (5) iron becomes cofactor some enzymes which are important for synthesis of collagen (Wild et.al., 2010).[15]

2. Local treatment

a. Dressing

There are lots of types of dressing which used in DFU. However, dressings usually tend to apply by general practitioners based on professional experiences or preference more than based on evidence-based studies. Therefore the study developed in UK tries to compare the effectiveness of three common dressing used in UK. This study compared the efficacy of fibrous-hydrocolloid (aquacel) dressing, iodine-impregnated dressing (Inadine), non adherent dressing, viscose filament gauze (N-A). Involved 317 participants, this RCT studies selected respondents by inclusion and exclusion criteria and divided into three groups.

All of groups have same treatment except the dressing. Dressing changed applies daily or 3 times a week used current guidelines for practice including debridement and offloading. The result showed that, after 12 weeks N-A 25.5%, Aquacel 28.2%, and Inadine 29.6% of patients present healing. So for this result Inadine which is iodine-impregnated dressing proved become dressing product that most improved DFU healing (Jeffcoate et al., 2009). Not only modern dressing, alternatives dressing used natural product also found effective to improve wound healing. A Prospective RCT, double-blinded study used Manuka honey-impregnated dressing in the treatment of neuropathic diabetic foot ulcers. Thirty-two participants in treatment group treated by MHID (Medihoney Tulle Dressing) and another thirty-one treated with conventional dressing.

Preparation and wound care were applied by staff nurses in a daily basis. Participants follow 16 weeks intervention whether treatment group and control group. The result showed that mean healing time significantly differences between 2 groups ($p< 0.05$). Moreover, 78% participants in treatment group presented sterile ulcers in 1st week of follow up and in control group only showed 35% participants showed sterile wound in 1st week of follow up (Kamaratos, et al., and 2014). Therefore, Manuka honey-impregnated dressing is safe and proved to improve wound healing time. Moreover, it keeps the wound in sterile condition longer than conventional dressing. One study in Iran by Mohajeri, et al. (2014) conducted study about effectiveness pure extract kiwi fruit dressing to improve DFU healing.

54 respondents were assigned into two group, 17 respondents in study group and 37 in control group. Both of study group and control group received same standard treatments (regular sterile dressing with normal saline, surgical debridement, oral antibiotic and blood sugar control). The result showed study group can improve wound healing in terms of ulcer size and wound closure. Study group showed significant differences with the control group in both ulcer size and wound closure.[15]

Table 1: Classification of Advanced Wound Dressings Used for Diabetic Foot Ulcers Healing.[16]

Type	Example	Explanation	Advantages	Disadvantages
Hydrocolloids	Duoderm Granuflex Comfeel	Dressings usually composed of a hydrocolloid matrix bonded onto a vapor permeable film or foam backing. When in contact with the wound surface, this matrix forms a gel to provide a moist Environment.	Absorbent; can be left for several days; aids autolysis	Concerns about use for infected wounds; may cause maceration; unpleasant odor
Hydrogels	Aquaform Intrasite Gel Aquaflo	These dressings consist of cross-linked insoluble polymers (i.e., starch or carboxy methylcellulose) And up to 96% water. They are designed to absorb wound exudate or rehydrate a wound, depending on the wound Moisture levels. They are	Absorbent; donate liquid; aid autolysis	Concerns about use for infected wounds; may cause maceration; using for highly exudative wounds

		supplied in flat sheets, an amorphous hydrogel, or as beads		
Foams	Allevyn Cavicare Biatain Tegaderm	These dressings normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface	Highly absorbent and protective; manipulate easily; can be left up to 7 days; thermal insulation	Occasional dermatitis with adhesive; bulky; may cause maceration
Films	Tegaderm Opsite	Film dressings often form part of the construction of other dressings, such as hydrocolloids, foams, hydrogel sheets, and composite dressings, which are made of several materials with film being used as outer layer	Cheap; easily manipulated; permeable to water vapor and oxygen but not to water microorganisms	May need wetting before removal; not suitable for infected wounds; nonabsorbent; if fluid collects under film it must be drained or the film is replaced
Alginates	Calcium alginate dressing Kaltostat Sorblgon Medihoney	The alginate forms a gel when in contact with the wound surface, which can be lifted off with dressing removal or rinsed with sterile saline; bonding to a secondary viscose pad increases the absorbency	Highly absorbent; bacteriostatic hemostatic useful in cavities	May need wetting before removal
Silver impregnate	Acticoat Urgosorb Silver	These dressing are used to treat infected wounds, as silver ions are thought to have antimicrobial properties.	Antiseptic, absorbent; reduce odour improved pain-related symptoms; decrease wound exudates; prolonged dressing wear time.	High cost

Source: Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management and evaluation on diabetic foot ulcer. World J Diabetes. 2015; 6(1): 37-53.

b. Ischemic Preconditioning (IPC)

Performing IPC in healthy patients proved to demonstrate augmentation potential of blood endothelial progenitor cells. Moreover, IPC showed mobilized stem cell which improved number of peripheral blood stem cells. RCT conducted in Israel revealed that IPC became effective to improve wound healing.

Forty participants followed this study and they were divided into 2 group: IPC group and sham group. All participants receive standard wound care delivered by staff of clinic. Pressure cuffs applied in both arms and inflated and deflated 3 cycles of 5 minutes each. The pressure was different between both groups. In IPC group cuffs inflated 200 mmHg, in another hand, the sham procedure only gave 10 mmHg.

All participant followed 6-week intervention and examined every 2 weeks. The result showed significant differences between 2 groups. A number of 41% participants in IPC group reached complete healing in 6 weeks. On the other hand, there are no participants reached complete healing in 6 weeks (Shaked, et al., 2015).[15]

c. Oxygen-ozone Treatments

Oxygenation is important for wound in order to improve healing outcome. In DFU, tissue hypoxia due to lack of peripheral oxygenation is noted in problem of wounds. Ulcer tissue oxygenation is essential and might be influenced healing out-come. RCT conducted in China by Zhang, et al. (2014) showed that oxygen-ozone treatment improved wound healing and increase collagen fibers of the wound. The study group of this research received standard treatment which same as control group.

After debridement, respondents in study group received noninvasive oxygen-ozone treatments 30 minutes for 20 days. The oxygen supplied by using the ozone generator device with 52 µg/ml ozone in a special bag. After 20 days intervention, the study group showed significant wound healing compare with control group. Moreover, oxy-gen-ozone treatment also increased collagen fibers in site of wound.[15]

d. Offloading

Lower limb neuropathies lead to development of foot shear or broken skin. It is due to increased pressure in the same site of the plantar foot and neglected by diabetic patients. In concept of management of DFU, off-load plantar foot from frequent pressure is important to prevent foot shear.

Offloading nowadays is widely used because of some study proved the efficacy of offloading help to promote wound healing. A systematic review of management of DFU mentioned that elevated pressure of plantar foot significantly improved foot ulcer. Total Contact Cast (TCC) was claimed to be the most effective method of offloading currently (Alexiadou & Doupis, 2012). Moreover, some study compared the effectiveness of TCC compare with another method. One RCT examined the efficacy of TCC, removable boot with a shear-reducing footbed (SRB) and healing sandal (HSS).

Total 73 participants divided into three groups and received treatment within 12 weeks. The result proved that TCC became the most effective offloading method according to proportion of wound healing and fastest healing time (Lavery, et al., 2015).[15]

PREVENTION

Prevention of an initial or subsequent foot lesion is crucial to avoiding amputation.[17, 18, 19,] The best approach is to make use of a team of multidisciplinary professionals who are committed to limb salvage.Centers that have instituted teams specifically for this purpose have subsequently reported dramatic reductions in lower-extremity amputation and improved rates of primary-ulcer healing.[20, 21] Patient education has a central role in treatment and should include instruction on foot hygiene, daily inspection, proper footwear, and the necessity of prompt treatment of new lesions.[17, 18, 19]

Regular foot-care examinations, including debridement of calluses and ingrown toenails, provide an opportunity to reinforce appropriate self-care behaviors and allow for early detection of new or impending foot problems.[22, 23] Therapeutic shoes with pressure-relieving insoles are an essential element of ulcer prevention and have been associated with significant reductions in their development.[24, 25, 19] Elective surgery to correct structural deformities that cannot be accommodated by therapeutic footwear can be performed as needed in certain patients.[26, 27, 28] Common procedures include hammertoe repair, metatarsal osteotomies, plantar exostectomies, and Achilles tendon lengthening.[22, 28]

In patients with neuropathy, these procedures can be easily performed under local anesthesia. Working in unison with a vascular surgeon, these foot-sparing reconstructive procedures can even be performed after revascularization in an ischemic patient who might otherwise have needed amputation.[27]

CONCLUSION

Diabetes foot ulcer is one of serious complication in diabetes and its incidence is rapidly increased. Appropriate management of each factor believed can reduce the incidence of foot ulcer. However, some factors like age and duration of DM are not modifiable so patients and nurses should be concerned about that condition.[15]

Not all diabetic foot complications can be prevented, but it is possible to dramatically reduce their incidence through appropriate management and prevention programs. The multidisciplinary team approach that combines the expertise of many types of health care providers for diabetic foot disorders has been demonstrated as the optimal method to achieve favorable rates of limb salvage in the high risk diabetic patient.[28]

REFERNCES

1. Brodsy JW. The diabetic foot. In: Coughlin MJ, Mann RA, eds. Surgery of the Foot and Ankle. St Louis, MO: Mosby; 1999: 895–69. Wagner FW Jr. Management and treatment program for diabetic, neuropathic, and dysvascular foot problems. In: Instructional Course Lectures: Vol. 28. St Louis, MO: The American Academy of Orthopedic Surgeons. 1979. p. 143–65.
2. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: National Diabetes Data Group (U.S.). Diabetes in America. 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 1995.p. 95–1468. Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, et al. Diabetic foot disorders: A clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg 2000; 39(5 suppl): S1–60.

3. Journal Keperawatan Indonesia, Volume 21 No.2, July 2018, hal 84-93 pISSN 1410-4490, eISSN 2354-9203 DOI: 10.7454/jki.v21i2.634. Management Of Diabetic Foot Ulcer: A Literature Review. Angger Anugerah Hadi Sulistyo* Insan Cendekia Husada School of Health Science, Bojonegoro 62111, Indonesia.
4. Diabetic Foot Ulcer Oliver TI, Mutluoglu M. https://www.ncbi.nlm.nih.gov>books. Diabetic Foot Ulcer -stat pearls- NCBI Bookshelf.
5. Fed Pract. 2016 Feb; 33(2): 16–23. PMCID: PMC6368931 PMID: 30766158. Management of Diabetic Foot Ulcers: A Review. Robert G. Frykberg, DPM, MPH and Jaminelli Banks, DPM.
6. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217-28.
7. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, Wagner EH. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999; 22: 382-7.
8. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM; American Diabetes Association. Preventive foot care in diabetes. Diabetes Care 2004; 27: S63-4.
9. Boulton AJM, Vileikyte L, Ragnarson G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005; 366: 1719-24.
10. Diabetic Foot Ulcer Oliver TI, Mutluoglu M. https://www.ncbi.nlm.nih.gov>books. Diabetic Foot Ulcer -stat pearls- NCBI Bookshelf.
11. Strandness DE, Priest RE, Gibbons GW. Combined clinical and pathological study of diabetic and nondiabetic peripheral arterial disease. Diabetes 1964; 13: 366-72.
12. LoGerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N Engl J Med 1984; 311: 1615-9.
13. Kozak GP, Giurini R. Diabetic neuropathies: lower extremities. In: Kozak GP, Campbell DR, Frykberg RG, Habershaw GM, editors. Management of diabetic foot problems. 2nd ed. Philadelphia: WB Saunders; 1995. p. 43-52.
14. Gabbay KH. The sorbitol pathway and the complications of diabetes. N Engl J Med 1973; 288: 831-6.
15. Journal Keperawatan Indonesia, Volume 21 No.2, July 2018, hal 84-93 pISSN 1410-4490, eISSN 2354-9203 DOI: 10.7454/jki.v21i2.634. Management of Diabetic Foot Ulcer: A Literature Review. Angger Anugerah Hadi Sulistyo* Insan Cendekia Husada School of Health Science, Bojonegoro 62111, Indonesia.
16. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of Diabetic foot ulcer. World J Diabetes. 2015; 6(1): 37–53. [PMC free article] [PubMed] [Google Scholar].
17. Frykberg RG. Diabetic foot ulcers: current concepts. J Foot Ankle Surg 1998; 37: 440-6.
18. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. Am FAM Physician 1998; 57: 1325-32.
19. Frykberg RG. Team approach toward lower extremity amputation prevention in diabetes. J Am Podiatr Med Assoc 1997; 87: 305-12.
20. Holstein PE, Sorensen S. Limb salvage experience in a multidisciplinary diabetic foot unit. Diabetes Care1999; 22(suppl 2):B97-103.
21. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes Care 1999; 22: 1428-31.
22. Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, et al. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg 2000; 39(5 suppl): S1-60.
23. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. Diabetes Care 1999; 22: 1354-60.
24. Frykberg RG. Diabetic foot ulcerations. In: Frykberg RG, Ed. The high risk foot in diabetes mellitus. New York: Churchill Livingstone, 1991: 151-95.
25. Cavanagh PR, Ulbrecht JS, Caputo GM. New developments in the biomechanics of the diabetic foot. Diabetes Metab Res Rev 2000; 16(suppl 1): S6-10.
26. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990; 13: 513-21.
27. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med 1994; 331: 854-60.
28. Catanzariti AR, Blitch EL, Karlock LG. Elective foot and ankle surgery in the diabetic patient. J Foot Ankle Surg 1995; 34: 23-41.