REVIEW

Bali Dermatology and Venereology Journal (*BDV*) 2021, Volume 4, Number 2, 23-27
ISSN.2622-5417

Management of diabetic foot ulcers: dermatology perspective

Published by
Department of Dermatology and
Venereology, Universitas Udayana

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Submit: 2021-06-08
Accepted : 2021-08-23
Publish: 2021-12-30

ABSTRACT

Diabetes mellitus (DM) is a chronic and complex disease that affects various parts of the body. It can lead to multiple systemic complications and also cutaneous manifestation. Diabetic foot ulcer (DFU) is one of the most devastating complications of DM in dermatology. The main etiology is an increase in plasma glucose, risk factors, or comorbidities due to DM itself. Neglected DFU can lead to further complications, including high amputation and mortality rates; thus, the healing of ulcers is the main objective of the treatment. Management is divided into the standard of care and adjuvant therapies. This study aims to optimize DFU management, so it can provide proper treatment and prevent complications.

Keywords: Diabetes mellitus, diabetic foot ulcers, management.
Cite This Article: Daryago, A.A.A., Fitriani., Kartowigno, S., Aryani, I.A., Yahya, Y.F., Diba, S., Stephanie, A. 2021. Management of diabetic foot ulcers: dermatology perspective. *Bali Dermatology and Venereology Journal* 4(2): 23-27. DOI: 10.15562/bdv.v4i2.65

INTRODUCTION

Diabetes mellitus is a metabolic disorder syndrome characterized by increased fasting plasma glucose 126 mg/dL or temporary plasma glucose ≥200 mg/dL or HbA1C levels 48 mmol/mol. In the United States, DM is a chronic disease that contributes to increased morbidity and mortality every year.[1] The prevalence of DM in South Sumatra was 33,566 cases, and specifically in Palembang reached 6,590 points.[2] DFU is one of the implications for disorders in dermatology, especially in patients with DM. Around 15-25% of DFU patients have 10-30 times the risk of lower limb amputation.[1] It is chronic, complex, and often accompanied by infections and other comorbidities, thus requiring multidisciplinary care in a hospital.[3] Sinulingga. et al. reported more than 50% of type II DM patients were hospitalized accompanied by DFU.[4] The etiology of DFU is multifactorial, involving peripheral neuropathy, pressure, and repetitive trauma.[1] The principles of management are control plasma glucose, wound off-loading, local ulcer care, restoring tissue perfusion, and eliminating the infection.[5] The DFU management needs multidisciplinary care.[6] In dermatological practice, the dermatologist should be familiar with the standards of care and prevention of DFU, according to several books in dermatology.

PATHOGENESIS

The main etiology of DFU is metabolic disorders due to uncontrolled plasma glucose.[7] Neural cell damage is a complication of uncontrolled hyperglycemia that leads to neuropathy. Motor neuropathy results in impaired movement of the muscles and joints of the foot to perform flexion or extension foot deformities.[8,9] In autonomic neuropathy, dysfunction of the sweat and sebaceous glands thus the surface of the epidermis becomes dry, and fissures. Sensory neuropathy causes loss of sensory perception. Repeated trauma, dry skin, and fissures can result in impaired skin integrity and become a port of the entry for microbes. This has implications for further complications and increases the risk of amputation.[8]

Chronic increase in plasma glucose results in endothelial cell dysfunction, resulting in decreased capillary vasodilation and decreased nitric oxide (NO) synthesis. This condition is followed by persistent vasoconstriction and plasma hypercoagulation in the femoropopliteal artery and aortoiliac artery, thus impaired tissue perfusion, ischemia, and ulcers.[6,7] Elevated plasma glucose is an ideal condition for the growth of bacteria. The condition of DFU accompanied by infection results in disruption of the wound healing and increased amputation. High plasma glucose level results in immunological disorders, including increased apoptosis of T cells, proinflammatory cytokines, PMN cell dysfunction, impaired fibroblast proliferation, and migration of keratinocytes.[7]

MANAGEMENT

The management of DFU is divided into the standard of care and adjuvant therapy to improve wound healing, reduce pressure, and prevent recurrences.[10]

STANDARD OF CARE

Control plasma glucose

Controlled plasma glucose improves the wound healing process, prevents damage increases the response of the cellular immune system, reduces the risk of lower limb amputation.[6] Lane et al. showed that HbA1C levels 64 mmol/mol and fasting plasma glucose levels 126 mg/dl will increase the risk of amputation.[11]

Wound off-loading with ulcer protection

Wound off-loading is an attempt to reduce the "load" at the site of ulceration. The principles are ulcer protection with limits joint movement. It aims to prevent repeated trauma, distribute plantar pressure, protect the wound area, assist the wound healing process and prevent the recurrence of DFU. The total contact casting (TCC) method is the main choice for DFU, which is specially designed to suit the anatomical structure of the lower leg, including the sole and foot joints.[12] This cast is modified by using special cotton pads on the inner layer to protect the bony prominences from trauma and injury. The use of TCC is regularly changed at intervals of 3-7 days.[13] The mechanism of action is to reduce, redistribute the pressure of the forefoot up to 87% through the plaster adhesive wall and limit joint movement.[14] Merheb et al., Sudhi et al. showed 75% of patients had completely epithelialized after 4-6 weeks using TCC.[15,16]

Local ulcer treatment

DFU care for DM patients is education, selection of dressings, and debridement, especially surgical debridement.[5] DFU patients need to be always educated to carry out routine inspections of the soles of the feet every day, wash feet regularly with soap and water with a temperature below 37^0 C, use moisturizers, socks, footwear, and nail cutting. If there are callus, blisters, blisters, dermatitis, impaired nail growth, or infection, the patient should be advised to seek treatment.[1]

Wound dressing is an attempt to reduce exudate and create an ideal moist environment for wound healing. The purpose is to induce granulation process, autolytic debridement of necrotic tissue, angiogenesis, and migration of keratinocytes.[6] Dressings can also be used as a protective layer for wounds against trauma and infection.[17] The ideal criteria for wound dressings are long-lasting, easy to use, easy to adhere to without damaging the base, comfortable, inexpensive, and its use is following clinical conditions.[18] There are several modern dressing options recommended for ulcers with excessive exudates, such as foam adhesive, alginate, and hydrofiber. In ulcers without exudate using acrylic, hydrocolloid, or films. The main advantages of this dressing are that it can be used for a long duration, has better absorption ability, is painless, and does not cause trauma at the time of replacement, thereby reducing the time of hospital visits.[17]

Wound debridement eliminates necrotic, damaged, or infected tissue that is incompatible with the wound healing process.[12] The purpose of debridement in the DFU is to improve the wound healing process by forming new granulation tissue, re-epithelialization, and redistribution of pressure due to callus.[17] There are several types of debridement, but surgical debridement is the method that has been recommended as a standard of care DFU based on the Infectious Disease Society of America (IDSA) and the Wound Healing Society (WHS).[6] It is the fastest, most efficient, and selective debridement. This method is indicated for progressive DFU or recalcitrant, large lesion size, requires a biopsy sample, and there is a callus or abscess.[12]

Restore tissue perfusion

Good tissue perfusion is required for wound healing. Impaired tissue perfusion is often associated with peripheral arterial disease (PAD), which is asymptomatic, making it difficult to detect.[12] Routine vascular examinations should be performed at each patient visit by palpating the femoral, popliteal, posterior tibial, and dorsalis pedis arteries.[18] If no pulse is palpated from one of these arteries, a further examination should be recommended. Multidiscipline care is needed in the management of DFU.[1,6]

Eliminate infection

Infection may increase morbidity, inhibit the wound healing process and increase the risk of amputation.[7]

Early detection and selection of antibiotics are important in the management approach.[6] The diagnosis of DFU with infection can be established based on clinical manifestations, including erythema, warmth, edema, pain, or purulent secretions.[6] DFU patients with neuropathy or PAD are required by conducting an assessment based on secondary clinical manifestations, such as ulcer undermining, friable granulation tissue, foul odor, or increase in the amount of exudate.[3,18] The development of DFU with infectious conditions is growing rapidly, so empirical treatment can be applied. The choice of antibiotic use needs to pay attention to the severity of the infection and microbiological culture results.[3] Antibiotics are given for two weeks for mild degrees and 2-3 weeks for moderate-severe degrees.[7] Based on epidemiological research, the most common pathogens found in DFU with infection are Gram-positive cocci, especially *S. aureus* and *S.epidermidis*. Other pathogens are Gram-negative cocci bacteria, such as *E. coli*, *K. pneumonia*, and *P. aeruginosa*, while anaerobic bacteria, such as *Peptostreptococcus spp*, *Bacteroides spp*, *Prevotella spp*, and *Clostridium spp.*[6]

ADJUVANT THERAPY

Non-surgical debridement

The debridement method is divided into several ways, namely surgical and non-surgical, such as mechanical, autolytic, enzymatic, and biologic debridement. Wet-to-dry or simple saline dressings have a good mechanical debriding action and help in wound-bed preparation. The advantages are absorptive as well as adherent and inexpensive. However, they require frequent dressing changes (two to three times per day) depending on the type and severity of the wound. This method is often referred to as conventional dressing.[12,18]

Autolytic debridement is a method of

debridement of necrotic tissue and eschar by creating a moist environment in the wound area. Its mechanism of action is to hydrate, soften and liquefy necrotic tissue and eschar. Autolytic debridement is not recommended for DFU in the presence of infection or gangrene. This method requires secondary or semi-occlusive dressings with the addition of hydrocolloids or hydrogels.[12,18] Hydrogel is an insoluble polymer dressing that can bind relatively large amounts of water. The hydrogel can absorb exudate and distribute water to the wound area, thereby increasing wound moisture. The moist environment provides optimal conditions for cellular migration and facilitates autolytic through endogenous proteolytic enzymes.[6] The advantages are painless, do not damage wound tissue, provide a cooling effect. It's applicable in the joint area, deep, dry, or exudative ulcers.[19] Hydrocolloids are hydrophilic carboxy parts and hydrophobic bound to a polyurethane film. It is self-adherence, long wear time, and is impermeable to fluids. However, it is expensive low absorptive capacity, has potential trauma with removal, and may cause allergies. Alginates originate from seaweed. They are hemostatic and fluidly bound to external fibers. But they need a secondary dressing. Foam adhesive is polyurethane foam fluid exchange with partial fluid retention. The benefits are absorbant, and different pore sizes will give partial retention, but it is bulky and can macerate the surrounding skin. Saco et al. compared several modern dressings (alginates, hydrocolloids, hydrogels, foams) with conventional as an adjunctive treatment for DFU and venous ulcers. The results showed the same efficacy in both dressings, but the hydrogel efficacy was found to be superior ($p<0.001$).[19]

Enzymatic debridement is an enzyme-based debridement method, such as trypsin, papain, fibrinolysin-DNase, collagenase, papainurea, and streptodornase, which function as proteases of necrotic tissue. This method is recommended for DFU with infection, slough, necrotic tissue, and contraindications to surgical debridement.[12,18] Clostridial collagenase ointment (CCO) is an example of a topical enzymatic debridement agent. The content of collagen proteinase in CCO can improve the healing process through the induction of re-epithelialization and granulation tissue. This enzyme can specifically degrade collagen types I-IV.[20] In vitro studies have been shown to induce keratinocyte proliferation and migration.[21] Motley et al. showed the effectiveness of CCO. There was a significant improvement both clinically and statistically ($p<0.0001$) in the CCO group characterized by wound closure the DFU lesion area up to 62% in 6 weeks.[20]

Biological debridement is a method using fly larvae as maggot therapy in a sterile environment for medical purposes.[18] It is often used in chronic wounds to eliminate necrotic tissue bacteria and stimulate granulation tissue.[22] The maggot therapy has been shown to reduce bacterial colonization, regulate protease enzymes, degrade extracellular matrix (ECM), increase fibroblast migration and tissue perfusion.[6] The larvae produced enzymes, such as trypsin, collagenase, and chymotrypsin, which function to degrade necrotic tissue. This method also eliminates microorganisms that are resistant to antibiotics, such as *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and MRSA.[22] Pinheiro et al., Malekian et al. showed improvement in the DFU according to the improvement of granulation tissue, wound closure, decreasing colonization of *S. aureus* and *P. aeruginosa,* thus increasing DFU drainage.[22,23]

Current topical agents

In recent decades, nanocrystalline silver (nAg) and manuka honey have become increasingly popular as topical agents to increase wound healing.[6] The nAg as an antibacterial could be easily perforate bacterial cell walls, resulting in impaired cell membrane permeability. The nAg is also known as an anti-inflammatory through the suppression of several inflammatory cytokines and protease enzymes. Manuka honey as an antibacterial has acidic, hyperosmolar, and phytochemical properties that can lead to selective cellular dehydration.[24] Tsang et al. assessed the effectiveness of nAg, manuka honey compared to conventional dressings for 12 weeks. The results showed that the improvement in lesion size in the nAg group ($p<0.0005$) was 98% superior to manuka honey and conventional dressings. The average improvement in DFU was 81.8% in the nAg group, 50% in the manuka honey group, and 40% in the conventional dressing group.[24]

Growth factors are molecules that can regulate cellular differentiation to repair damaged tissue. These molecules act as inductors of cellular proliferation, migration, chemotaxis, and ECM formation. In infected DFU, there is a decrease in epidermal growth factors (EGF), thus increasing local plasma glucose levels, non-enzymatic glycosylation, and the formation of advanced glycation end products (AGEs). Epidermal growth factors function as negative feedback on the non-enzymatic glycosylation process so that the wound healing epithelialization process can run normally.[25]

The fibroblast growth factor (FGF) is an inductor of fibroblast proliferation and migration of vascular endothelial growth factor (VEGF) to the wound area. In DFU patients, the level of AGEs formation is known to increase. It inhibits cellular proliferation, the formation of granulation tissue, and prolonged inflammatory reaction so that the function of fibroblasts, VEGF, and keratinocytes are disrupted. The mechanism of action of FGF is to inhibit the binding of AGEs around the wound and accelerate the wound healing process.[25] Platelet-rich plasma consists of several growth factors that play a role in wound healing, such as EGF, FGF, VEGF, platelet-derived growth factor (PDGF), endothelial cell proliferation (ECGF), and transforming growth factor-beta (TGF-β). These growth factors function as stimulators of the proliferation of keratinocytes, fibroblasts, endothelial cells, angiogenesis, ECM, and collagen synthesis, which are important in the wound healing process.[26]

Xu et al. compared the use of single growth factor EGF, FGF, and combined growth factor (EGF-FGF) to the conventional dressings. Complete closure of the DFU lesion was achieved for 36 days faster in the combination group ($p<0.01$), EGF for 39 days ($p<0.05$), FGF, and the control group required a longer duration. The combined growth factors lead to a faster duration of improvement in DFU.[25] Babaei et al. reported the success rate of

PRP in DFU patients. It was complete wound closure (100%) in 7.5-8.5 weeks.[27] Hirase et al. showed the effectiveness of PRP, which is rapidly wound closure ($p<0.0001$) than the conventional dressings.[28]

Skin graft

A skin graft is an act of transferring or transplanting skin tissue from a donor to a recipient with the aim of closing defects or wounds caused by surgery. In addition, this action can also be used as a treatment for chronic ulcers, burns, epidermolysis bullosa, and vitiligo. Skin grafts are categorized into three types, namely autograft, allograft, and xenograft.[29] The mechanism of action of skin grafts is to increase angiogenic amplification through proliferation and migration of endothelial cells. Skin grafts can also induce the production of endogenous angiogenic growth factors that can help the wound healing process, such as VEGF, PDGF, FGF, and EGF.[30] Tettelbach et al. assessed the effectiveness of skin grafts from dehydrated human amnion/chorion membrane (dHACM) in DFU. There was an improvement which was assessed as faster as indicated by complete lesion closure in the dHACM group (81%).[30]

Hyperbaric oxygen

One of the comorbidities of DM that play a role in the formation of DFU is macro and microangiopathy. This causes the oxygen supply to the wound area to decrease and tissue to become hypoxic. This condition can increase the risk of bacterial infection and further tissue damage.[31] Oxygen plays an important role in the wound healing process related to functions in cell proliferation, collagen synthesis, reepithelialization, and the body's defense against bacteria. Hyperbaric oxygen is a modality to assist the binding and release of oxygen through the diffusion of hemoglobin molecules into hypoxic tissues.[31] Hyperbaric oxygenation can inhibit the production of proinflammatory cytokines, which can induce apoptosis.[32] Hunt et al. assessed the effectiveness of local use of hemoglobin spray (HS) in DFU patients. Repair of lesions at week 4 in the HS group reached 63% and at week 28 increased to 95% ($p<0.05$). Slough elimination was complete in the HS group compared to controls ($p<0.001$). The HS can also help reduce pain.[31] Chen et al. reported the success of this method based on the improvement of the inflammatory process, improved tissue perfusion quality of life and reduced the risk of amputation.[32]

Negative-pressure wound therapy

Negative-pressure wound therapy (NPWT) is a non-invasive therapeutic modality that can assist the wound healing process using a vacuum-assisted closure (VAC).[33] This device is indicated for recalcitrant DFU.[34] This is related to the VAC system that can pull exudate from the wound tissue and reduce edema so that interstitial pressure decreases microvascular occlusion is reduced, and the lymphatic flow returns to normal. Protease enzymes are known as basic components of wound tissue exudates, so VAC is needed to eliminate and balance the excess of these enzymes.[33] In vitro studies have shown that mechanical stress on NPWT has been shown to increase protein kinase p38, several transcription factors, and CD 31. This molecule is a protein marker of angiogenesis and leukocyte migration processes.[33] The NPWT device is also occlusive so that it can create a moist atmosphere around the wound and make an ideal environment for cellular reepithelialization.[33]

Energy-based device

Electrical stimulation (ES) is a technique used to increase the influx and permeability of cell membrane calcium channels, thereby inducing NO synthesis. NO function as a vasodilator can increase blood flow, intracellular glucose transfer, migration of fibroblasts, keratinocytes, macrophages, epithelialization, activate VEGF and collagen synthesis.[9] Extracorporeal shockwave therapy (ESWT) is an energy-based modality that can stimulate wound healing through the synthesis of NO and VEGF, promoting vascular vasodilation and angiogenesis.[6] It is proven based on histopathological, including several growth factor molecules, neovascularization, and blood cells.[34] The few RCTs comparing ESWT with standard care are small and show variable efficacy.[6] Huang et al. showed that ESWT was effective in increasing epithelialization and wound healing in DFU.[34] Laser therapy promotes the reduction of inflammation, angiogenesis, and production of extracellular matrix components. CO2 laser therapy is found to significantly reduce wound bacterial load.[6]

CONCLUSION

Negligence of ulcers in diabetic patients may cause amputation and death. The standard of care is the primary principle, whereas adjuvant therapy is also important to achieve complete healing. Management at the DFU requires good collaboration and communication between patients and health care workers, in particular multidisciplinary medical specialists.

CONFLICT OF INTEREST

None declared.

FUNDING

None.

AUTHOR CONTRIBUTION

All authors contributed from literature review, manuscript construction to publication.

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