Review Article

**Etiology, pathophysiology, diagnosis and management of diabetics’ foot ulcer**

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**ABSTRACT**

Diabetic foot ulcers (DFU) is a lesion of all layers of skin, necrosis or gangrene that occurs in the soles of the feet in diabetes mellitus (DM) patients, caused by: (1) causative factor (peripheral neuropathy, high foot plantar pressure and trauma); (2) contributive factors (atherosclerosis and diabetes). The treatments of diabetic ulcers consist of determining and repairing the underlying cause of ulcer, good wound care and prevention of ulcer recurrence. The cause of diabetic ulcers can be determined by deep anamnesis and physical examination. DFU therapy includes necrotomy/debridement, reducing the load/pressure on the offensive area, manage the infection by diagnosing the type of bacteria, providing adequate antibiotics and ulcer treatment using wound dressing clean and moist.

**Keywords:** Diabetes mellitus, Diabetic foot ulcers, Diagnosis, Epidemiology, Management

**INTRODUCTION**

Diabetic foot ulcers are an injury to all layers of skin, necrosis or gangrene that usually occur on the soles of the feet, as a result of peripheral neuropathy or peripheral arterial disease in diabetes mellitus (DM) patients. Understanding diabetic foot ulcers include necrosis or gangrene. Diabetic gangrene is a tissue death caused by a blockage of blood vessels (ischemic necrosis) due to micro emboli atherotrombosis which is caused by occlusive peripheral vascular disease that accompanies diabetics as a chronic complication of diabetes itself.

Diabetic foot ulcers can be followed by bacterial invasion resulting in infection and decay, can occur in any part of the body especially in the distal part of the lower leg. Incidence of DFU continues to increase worldwide. Research from Leone et al, showed that 15% of patients with DM will experience complications of DFU in the future. It seems that the prevalence of DFU is not accurately known and the difference in prevalence rates in each country, but is estimated at 4-27% of DFU sufferers worldwide.

The prevalence of diabetic ulcer patients in the United States is 15-20%, the risk of amputation is 15-46 more compared with non-DM patients. Prevalence of risk and DFU in Indonesia is estimated high, because the undiagnosed DM patients are high either. According to Waspadji, diabetic foot is one of the most feared chronic infections of DM, end stage with disability (amputation) and death. In Indonesia, mortality and amputation rates are still high at 16% and 25% respectively.

**Etiology of diabetic foot ulcers**

There are several components that cause the emergence of diabetic foot ulcers in diabetic patients, can be divided into two major factors, namely:
**Causative factor**

**Peripheral neuropathy (sensory, motor, autonomic)**

The main and most important causative factors. Sensory neuropathy is usually fairly deep (>50%) before experiencing a loss of protective sensation which results in susceptibility to physical and thermal trauma, thus increasing the risk of foot ulcers. Not only the sensation of pain and pressure are lost, but also the proprioception of the sensation of foot position also disappeared. Motor neuropathy affects all the muscles in the legs, resulting in protrusion of abnormal bones, normal architecture of the foot changed, distinctive deformity such as hammer toe and hallux rigidus. As for autonomic neuropathy or autosимпатectomy, characterized by dry skin, no sweating and increased secondary capillary refill due to arteriovenous shorts in the skin, triggering fissures, skin crust, all make the foot vulnerable to minimal trauma.

**High foot plantar pressure**

The second most important causative factor. This situation is related to two things: limitations of joint mobility (ankle, subtalar and first metatarsophalangeal joints) and foot deformities. In patients with peripheral neuropathy, 28% with high plantar pressure, within 2.5 years there will be a foot ulcer compared with patients without high plantar pressure.

**Trauma**

Especially recurring trauma, 21% trauma from friction from footwear, 11% due to foot injuries (mostly due to fall), 4% cellulitis due to tinea pedis complications and 4% due to fingernail cut errors.

**Contributive factor**

**Atherosclerosis**

Atherosclerosis due to peripheral vascular disease, especially regarding the blood vessels of femoropoplitea and small blood vessels below the knee, is the most important contributing factor. The risk of ulcers, twice as high in diabetic patients as compared to non-diabetic patients.

**Diabetes**

Diabetes leads to intrinsic wound healing, including collagen cross-linking disorders, matrix functional disorders and immunologic disorders, especially impaired PMN function. In addition, diabetics have higher rates of onychomycosis and tinea infections, so the skin is easy to peel and infections. In DM, characterized by sustained hyperglycemia as well as increased inflammatory mediators, triggering an inflammatory response, leading to chronic inflammation, but this is considered to be low-grade inflammation, since hyperglycemia leads to impaired cellular defense mechanisms. Inflammation and neovascularization are important in wound healing, but must be sequential, self-limited and closely controlled by the interaction of molecular cells. In DM, acute inflammatory responses are considered weak and angiogenesis is disrupted resulting in wound healing disorders.16 Wound healing disorders in diabetes are shown in Figure 1.

![Figure 1: Wound healing disorders in diabetes.](image)

**Pathophysiology of diabetic foot ulcers**

In DM patients there is an increased occurrence of the main risk of the occurrence and development of diabetic foot ulcers, namely peripheral neuropathy, peripheral vascular disease and disruption of response to infection. In addition, in DM there is a wound healing disorder that increases the risk of infection.17,18 Neuropathy in DM manifests against motor, sensory and autonomic. Damage to the innervation of the leg muscles causes an imbalance between flexion and leg extension, resulting in deformity and change of pressure points. Gradually, it will cause skin damage that develops into ulcers. Autonomic neuropathy lowers the activity of oil glands and sweat so that the foot moisture is reduced and susceptible to injury. Sensory neuropathy lowers the pain threshold so that it is often unaware of the existence of the wound until the wound worsens.17

In peripheral arteries, hyperglycemia causes endothelial dysfunction and blood vessel muscle, as well as decreased vasodilator production by the endothelium resulting in constriction. Hyperglycemia in DM increases thromboxane A2, namely vasokontriktor and aggregate platelet aggregates, resulting in an increased risk of plasma hypercoagulability. Hypertension and dyslipidemia also contribute to the occurrence of peripheral arterial disease. The explanation above will lead to occlusive arterial disease which then causes ischemia of the lower extremities and increases the risk of ulcers. The formed ulcers will be easily infected, develop into gangrene and end up with a lower leg amputation (below knee amputation).17,18
In DM, there is a decreasing in peripheral soft tissue healing ability that leads to ulcers. In diabetes, especially in the advanced stage where the structure of skin tissue, nerves, blood vessels and other support tissues have been damaged, so the control of blood glucose is no longer enough to fix them. Slow wound healing in DM will increase the risk of wound complications that will further slow wound healing. These complications include infections (including cellulitis, abscesses and osteomyelitis), gangrene and septicemia.\textsuperscript{18,19} Pathophysiology of diabetic ulcers can be seen in Figure 2.

![Figure 2: Pathophysiology of diabetic ulcers.](image)

### Types of diabetic foot ulcers

According to Edmon diabetic foot ulcers are divided into 2 groups, namely:\textsuperscript{21}

**Neuropathic ulcers**

Feet is warm, perfusion is still good with pulsation still palpable, perspiration is reduced, skin dry and cracked.

**Neuroischemic ulcers**

Feet is colder, not palpable pulsation, thin skin, smooth and without hair, subcutaneous tissue atrophy, intermittent claudication and rest pain may not be present due to neuropathy.

### Classification and degree of diabetic foot ulcers

There are several classifications of diabetic foot ulcers known today such as: Wagner classification, University of Texas wound classification system (UT) and PEDIS. Wagner's classification is widely used, describes the extent and weight of the ulcer but does not describe the state of ischemia and treatment initiatives.\textsuperscript{22,23} Criteria for diagnosis of infection in diabetic foot ulcers if there are 2 or more of the following signs: Swelling, induration, erythema around the lesion, local pain, palpable local warmth and presence of pus.\textsuperscript{24,25} Infection is divided into mild infections (superficial, inner and limited in size), moderate (deeper and wider), severe (accompanied by systemic signs or metabolic disorders).\textsuperscript{25}

Included in severe infections such as necrotizing fasciitis, gangrenous gas, ascending cellulitis, there is compartment syndrome, infection with systemic toxicity or metabolic instability that threatens the legs and psyche of the patient.\textsuperscript{26}

Classification of Wagner Grade 0 No ulcers in high risk leg patients, Grade I Premature superficial ulcer. Grade II Ulcer deeper, regarding tendons, ligaments, muscles, joints, not exposed to bone, without cellulitis or abscess. Grade III Deeper ulcers are already about frequent bone complications of osteomyelitis, abscesses or cellulitis. Grade IV Gangrene distal toes or toes. Grade V Gangrene whole legs.\textsuperscript{22} The PEDIS classification system is divided into 5 categories: Perfusion, Extent / size, Depth / tissue loss, Infection and Sensation.\textsuperscript{22,23} The classification of PEDIS is highly relevant to the pathogenesis and development of DFU.\textsuperscript{29}

### Clinical diagnosis of diabetic foot ulcers

Management of diabetic ulcers consists of determining and repairing the underlying cause of ulcer disease, good wound care, and prevention of ulcer recurrence. The cause of diabetic ulcers can be determined precisely through deep anamnesis and physical examination.\textsuperscript{30}

### History

Symptoms of peripheral neuropathy include hypesthesia, hyperesthesia, paresthesia, disesthesia, radicular pain and anhidrosis. Most people with atherosclerotic disease in the lower extremity are asymptomatic, patients who show symptoms are found claudicatio, ischemic pain at rest, non-cured wounds and obvious leg pain. Cramps, weakness and discomfort in the legs are often felt by diabetics because of their tendency to suffer from occlusion of tibioperoneal atherosclerosis.\textsuperscript{31,32}

### Physical examination

According to Stillman, physical examination in patients with diabetic ulcers is divided into 3 parts, namely:\textsuperscript{32}

#### Examination of ulcers and general circumstances of the extremities

Diabetic ulcers have a tendency to occur in some of the areas that become the largest loads of heels, such as the heel, the area of the metatarsal head on the palm, the prominent fingertips (on the first and second fingers).
Ulcers can arise in malleolus because in this area it often gets traumatized. Other abnormalities found in the physical examiner include: hypertrophic callus, brittle or broken nail, hammer toes and fissure.

Assessment of possible vascular insufficiency

Physical examination shows the disappearance or decrease of the peripheral pulse below a certain level. Other findings associated with atherosclerotic disease include bruits on the iliac and femoral arteries, skin atrophy, hair loss in the legs, cyanosis of the toes, ulceration and ischemic necrosis, both pale feet when the foot is raised as high as the heart for 1-2 minute. Noninvasive vascular examinations include measurements of transcutaneous oxygen, anklebrachial index (ABI), systolic pressure of the toes. Ankle brachial index is a noninvasive examination that is easily performed using the doppler tool.

Cuff pressure mounted on the upper arm and pumped until the pulse on the brachialis can not be detected by doppler. Then the cuff is released slowly until doppler can detect back the brachial pulse. The same action is performed on the legs, where the cuff is placed in the distal calf and the doppler is attached to the dorsalis pedis or posterior tibial artery. Ankle brachial index is obtained from ankle systolic pressure divided by systolic brachial pressure.15,33,34

Assessment of possible peripheral neuropathy

Peripheral neuropathy signs include loss of sensation of vibration and position, loss of deep tendon reflex, tropical ulceration, foot drop, muscle atrophy and hypertrophic callus formation especially in the pressure areas, on the heel for example. Neurologic status can be examined using the Semmes-Weinstein monofilament to determine if the patient still has a "protective sensation".

The examination shows abnormal results if the patient can not feel the touch of the monofilament when pressed on the foot with sufficient pressure until the monofilament is bent. Another checking instrument is a 128°C garputala, Which can be used to determine the sensation of vibration by examining the ankle and the first metatarsalphalangeal joint. In metabolic neuropathy there is an intensity gradient and the most severe in the distal region.

Thus, in patients who can not feel the vibration of the wrist when the rotation of the toe is removed from the toes to the wrist indicates intensity gradient because of metabolic neuropathy. Generally, can not feel the vibration of the garputala on the fingers more than 10 seconds after the patient can not feel the vibrations on the big toe. Some people with normal sensations only show the difference between the sensation of the toes with the examiner's hand for less than 3 seconds.15,32,33,35

Laboratory examination

• Blood tests: leukocytosis may indicate an abscess or other infection of the foot. Wound healing is inhibited by the presence of anemia. The presence of arterial insufficiency that already exists, the state of anemia causes pain at rest
• Metabolic profile: measurement of blood glucose, glychemhemoglobin and serum creatinine helps to determine the adequacy of glucose regulation and renal function
• Noninvasive vascular laboratory examination: pulse volume recording (PVR) or plethymosgraphy.

Radiological examination

• A plain examination of the diabetic foot may show demineralization and the charcot joint and the presence of osteomyelitis
• Computed tomographic (CT) scan and magnetic resonance Imaging (MRI): although an experienced examiner can diagnose an abscess with a physical examination, a CT scan or MRI may be used to help diagnose an abscess if the physical examination is unclear
• Bone scanning is still questionable for its usefulness because of the large false positive and false negative results. Recent research cites 99mTc-labeled ciprofolxacin as a marker for osteomyelitis
• Conventional arteriography: when vascular or endovascular surgery is planned, arteriography is necessary to show the extent and significance of atherosclerotic disease.

Alternatives to conventional angiography

• Magnetic resonance angiography (MRA): MRA is an alternative that can be used in high-risk patients or patients who are allergic to contrast material. The contrast used was Gadolinum chelates, potentially causing 3 side effects in patients with renal insufficiency: acute renal injury, pseudohipokalemia and systemic nephrogenic fibrosis.
• Multidetector computed tomographic angiography (MDCT) avoids arterial stabbing. By using intravenous contrast injection, multidetector CT scans (16 or 64 channels) can improve the resolution of angiographic images and at relatively high speeds. The use of contrast in MDCT has the same risk.
• Carbon dioxide angiography is an alternative to patients with renal insufficiency, but it is not widely applicable and still requires iodine contrast material as an additional carbon dioxide gas to obtain a good image.
• Plain radiography is not used for routine examination of occlusive peripheral arterial disease. This is because arterial calcification seen in plain radiographs is not a specific indicator of atherosclerotic disease. Calcification of the arterial media layer is not a diagnosis of atherosclerosis, and
even calcification of the intima layer, which is a diagnosis of atherosclerosis, will not cause significant haemodynamic stenosis.

**Management of diabetic foot ulcers**

The main goal in the management of diabetic ulcers is the closure of the wound.\(^{27}\) Treatment of DFU wound in DM patients is carried out constantly with the type of action depending on the severity of the ulcer and the presence or absence of ischemia. The basis of DFU therapy is: necrotoxy/ debridement, reducing the load/pressure on the area of the injury (offloading), manage the infection by diagnosing the type of bacteria, providing adequate antibiotics and ulcer treatment using wound dressing clean and moist.\(^{20,36,37}\)

**Debridement**

Debridement is an act of disposing of non-living materials, foreign bodies, and unhealthy tissues that are difficult to recover from injury.\(^{36}\) Debridement should be performed on all chronic wounds to remove necrotic tissue and debris.\(^{39,40}\)

This action is carried out by removing the base of abnormal injuries and wound edge tissue such as epidermal hyperkeratosis (callus) and necrotic dermal tissue, debris and bacterial elements that can inhibit wound healing. From several clinical trials studies, it was found that debridement plays a role in assisting wound healing through the production of granulation tissue.\(^{36,37,41}\)

Debridement is an important and decisive step in the handling of diabetic foot ulcers as a wound bed preparation effort by altering the local environment or milieu from a chronic wound into an acute wound to stimulate and accelerate the healing process of the wound.\(^{3,42-44}\) At the time of debridement, there is a new wound bleeding, so that the debridement action in diabetic foot ulcers will be able to increase VEGF levels according to the hypothesis of Frank et al.\(^{45}\) The frequent debridement of diabetic foot ulcers can increase the rate of wound healing, although there is not enough evidence to establish this opinion.\(^{46}\)

There are 5 types of debridement: surgery, enzymatic, auto lithics, mechanics and biologics, only surgical debridement has been shown to be effective in clinical trials. Surgical debridement is a sharp debridement to remove all dead tissue and bone. The purpose of debridement is to transform the chronic wound healing environment into acute wound healing. Enzymatic debridement, using specially tailored proteolytic enzymes such as collagenase, papain/urea from papaya, fibrinolysis/DNase, trypsin, streptokinase-streptodornase combination. Autolytic debridement, occurs naturally in healthy, moist and perfused ulcers. Mechanical debridement, performed physically by dry-wet dressing, pressure irrigation, lavage and hydrotherapy. Biologic debridement, using the sterile larvae of the Lucilia sericata fly, the larvae secrete a proteolytic enzyme that can dilute the necrotic tissue.\(^{38,47}\)

**Offloading**

In patients with lesions on the soles of the feet, it takes offloading through several methods or tools to shift the weight fulcrum away from the side of the ulcer. The purpose of this offloading is to prevent tissue trauma and facilitate wound healing.\(^{36,39}\) Offloading is a reduction in pressure on the ulcer, becoming one of the components of diabetes ulcer management. Ucleration usually occurs in the area of the foot that gets high pressure. Bed rest is an ideal way to reduce pressure but it is difficult to do total contact casting (TCC) is the most effective offloading method. TCC is made of specially formed casts to spread the patient’s burden out of the ulcer area.

This method allows the patient to walk during treatment and useful for controlling the presence of edema that can interfere with wound healing. Although difficult and long, TCC can reduce the pressure on the wound and it is shown by the healing of 73-100%. The disadvantages of TCC include skill and time, irritation from plaster can cause new injuries, difficulty assessing injuries every day, more use of Cam Walker, removable cast walker, allowing for daily wound inspection, dressing change and early infection detection. Some other methods that can be done include bed rest, the use of wheelchairs, walkers to shoes that are specially designed.\(^{48,49}\)

**Management of infection**

Diabetic ulcers allow bacterial entry, as well as infection of the wound. Because of the high incidence rate of infection in diabetic ulcers, a systemic approach is required for a complete assessment. The diagnosis of infection is primarily based on clinical conditions such as erythema, edema, pain, softness, warmth and discharge from pus.\(^{50}\) Determination of the degree of infection becomes very important. According to the infectious diseases the society of America divides the infection into 3 categories: (1) Mild infections: if erythema is obtained < 2 cm, (2) Moderate infection: if erythema is > 2 cm and (3) Severe infection: systemic infection.\(^{50}\)

Diabetic ulcers are divided into 2 groups, namely: (1) Non-limbal threats: cellulitis < 2 cm and does not extend to bone or joints and (2) Limb threatening: cellulitis > 2 cm and has bone and joints, and systemic infection.\(^{32}\) Research on the use of antibiotics as a therapy of diabetic ulcers is still less, only based on clinical experience. Antibiotic therapy should be based on bacterial culture results and the antibiotic’s toxicity capability.\(^{50}\)

In non-limb-threatening infections are usually caused by staphylococcus and streptococcus. Mild and moderate
infections may be treated for polymicrobes by oral antibiotics, such as cephalaxin, amoxilin-clavulanic, moxifloxin or clindamycin. In severe infections due to polymicrobial infection, such as staphylococcus, streptococcus, Enterobacteriaceae, pseudomonas, enterococcus and anaerobic bacteria e.g. Bacteroides, Pepto cocci, Pepto streptococci. In severe infections should be hospitalized, with antibiotics that include gram positive and gram negative, and aerobic and anaerobic.

The choice of intravenous antibiotics for severe infections includes imipenem-cilastatin, B-lactami B-lactamase (ampicillin-sulbactam and piperacilintazobactam) and broad-spectrum cephalosporin.31,32

Dressing

Dressing is a material used topically on the wound to protect the wound and help wound healing. Dressing will experience direct contact with the wound and is distinguished by plaster as a dressing barrier. There are several types of dressings: film, composite, hydrogel, hydrocolloid, alginate, foam and other absorptive dressings such as negative pressure wound therapy (NPWT).51,52

The main purpose of a closed-clean-wound or granulated wound is to provide a humid healing environment to facilitate cell migration and prevent dry sores. The choice of dressing depends on the number and type of exudate present in the wound. Hydrogel dressing, film, composite is well used for cuts with a small amount of exudate. For wounds with exudate amounts being used hydrocolloids and for wounds with exudate amount widely used alginate, foam and NPWT. Injuries with large necrotic tissue should be done debridement before dressing.51-53

Negative pressure wound therapy or wound closure with a vacuum using a sponge on the wound, covered an airtight dressing, then a vacuum is installed. Negative pressure wound therapy can be used for wounds with large lymphatic leaks and fistulas. The main mechanism of NPWT is to eliminate edema, NPWT removes the fluid of the lymph or the lymph in interstitial, thus increasing the diffusion of interstitial oxygen into the cell. Negative pressure wound therapy also eliminates collagenase and MMP enzymes that increase levels in chronic wounds.51,52

CONCLUSION

The incidents of diabetic foot ulcers will increase in the future and require a high cost of care. DFU healing also takes a long time and can lead to amputation in the lower extremities, thus exacerbating quality of life and increasing mortality.

Wound healing requires infection control, inflammatory repair, regeneration of connective tissue matrix, angiogenesis/vasculogenesis, wound constriction and reepithelization. Management of DFU management focused on prevention of amputation in lower limb with 3 strategies, namely: identification of risk factor of DFU, acute treatment and prevent complication. Therapy performed on the wound of the DFU is carried out constantly with the type of action that depends on the severity of the ulcer and the presence or absence of ischemia. The basis of DFU therapy are necrotomy/debridement, reducing offloading, managing the infection by diagnosing the type of bacteria and providing an adequate antibiotic, managing wound dressing clean and moist.

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