

# Pathophysiology diabetic foot ulcer

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**Abstract.** Diabetes Mellitus (DM) is known to have many complications. Diabetes and its complications are rapidly becoming the world's most significant cause of morbidity and mortality, and one of the most distressing is Diabetic Foot Ulcer (DFU). Chronic wound complications are a growing concern worldwide, and the effect is a warning to public health and the economy. The etiology of a DFU is multifaceted, and several components cause added together create a sufficient impact on ulceration: neuropathy, vasculopathy, immunopathy, mechanical stress, and neuroarthropathy. There are many classifications of the diabetic foot. About 50% of patients with foot ulcers due to DM present clinical signs of infection. It is essential to manage multifactorial etiology of DFU to get a good outcome.

## 1. Introduction

Diabetes mellitus (DM) is a complex disease affecting almost all the vital organs in the body. About 415 million people in the world diagnosed with DM and majority of them are due to DM type 2. DM incidence predicted to increase 642 million people by the year 2040.[1] DM is known to have many complications and one of the most distressing is Diabetic Foot Ulcer (DFU) which affects 15% of people with diabetes. Infections, chronicity, and recurrence are the opportunistic problem of DFU. they can affect the mind of the patient. The amputation decision is often in A benign-looking ulcer in a patient with diabetes. A research in the United States presented that 38% of all the amputations associated with DM. It can induce to advance morbidity and mortality. DFU puts the huge financial load on the patient and the healthcare services, even though it is preventable. The successful DFU management strategies involve intensive prevention, early assessment and aggressive treatment by a multi-disciplinary team of experts.[2,3]

## 2. Definition

Diabetic Foot Ulcer (DFU) is as a foot affected by *ulceration* that associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes.[4] The classical triad of DFU is neuropathy, ischemia, and infection. Impaired metabolic mechanisms in DM increased the risk of infection and poor wound healing. It happens due to series of mechanisms which include decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis. So, the feet are influenced by damage to peripheral nerves, the peripheral vascular disease, ulcerations, deformities, and gangrene. [3]

## 3. Epidemiology

Diabetic foot disease is a complication of diabetes associated with major morbidity, mortality, costs, and reduced quality of life. Diabetic foot disease typically presents as ulcers, infection, and Charcot



foot in the presence of peripheral neuropathy or peripheral arterial disease in people with diabetes, and is the most important precursor for lower-extremity amputations.[5-7]

By 2015 prevalence data from the International Diabetes Federation, it estimated that, annually, foot ulcers develop in 9.1 million to 26.1 million people with diabetes worldwide. The proportion of persons with diabetes and a history of foot ulceration is understandably higher than the proportion with an active ulcer; 3.1 to 11.8% of persons with diabetes, or 12.9 million to 49.0 million persons worldwide and 1.0 million to 3.5 million in the United States alone, have a history of foot ulceration. The lifetime incidence of foot ulcers has previously been estimated to be 15 to 25% among persons with diabetes, but when additional data are considered, between 19% and 34% of persons with diabetes are likely to be affected.[1,8]

Several previous studies held in Indonesia had documented the rate to be in the range of 17-32%, while the proportion of amputation was 15-30%. One-year survival following amputation can be as high as 14.8%, but the rate dramatically increases up to 37% in the next three years.[9]

Complications of the chronic wound are a bigger concern worldwide and its influence is a threat to public health and the economy. The growing global prevalence of diabetes affects all populations and is associated with obesity, impaired wound healing, and chronic DFU formation. Worldwide, the number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 with this “diabetic epidemic” continuing even if levels of obesity remain constant. Complications of Diabetic wound include soft tissue and bony wound infections, progressive tissue loss, lower extremity amputations, accelerated cardiovascular disease, and patient mortality. A common complication for patients with diabetes, the lifetime risk for lower extremity ulceration, is as high as 25%, with over 7% of individuals with diabetic neuropathic foot ulcers progressing to amputation.[10]

#### **4. Risk factor**

Previous studies have identified smoking as a risk factor for diabetic foot ulcers because daily tissue hypoxia may cause vascular and neuropathic disorders in the lower extremities of diabetic patients.[11] The contribution of obesity to the risk of diabetic foot ulceration is inconclusive. Previous studies have revealed that obesity might associate with diabetic foot ulcers.[12,13] However, there are also prospective studies showing that BMI has no significant correlation with a diabetic foot ulcer.[14] Zang *et al.* in their study suggested that patients with diabetic foot ulceration had lower BMIs than patients without a diabetic foot, and most BMI levels in our study ranged from 25 to 30 kg/m<sup>2</sup>. These results suggested that the association between BMI ranging from 25 to 30 kg/m<sup>2</sup> and diabetic foot ulcer requires further research. Their study also suggested that diabetic foot was more common in male diabetic patients than female patients. One explanation of this gender difference might be the involvement in increased physical work in males.[15,16]

#### **5. Pathophysiology**

The etiology of a diabetic foot ulcer (DFU) is multifaceted. No single risk factor is responsible for a foot ulcer. Several components cause added together to create a sufficient impact for ulceration.

#### **6. Neuropathy**

Peripheral neuropathy (loss of sensation) frequently occurs, 20% at the time of diagnosis and about 8-12 years after developing type 2 diabetes, and is the permissive factor in ulcer development. Diabetic peripheral neuropathy is an impairment of normal activities of the nerves throughout the body and can alter autonomic, motor, and sensory functions. The reported prevalence of diabetic peripheral neuropathy ranges from 16% to as high as 66%.[1]

More than 60% incidence of foot ulcers caused by Neuropathy and affects patients with both type 1 and type 2 DM. The hyperglycemic conditions increased the production of some enzyme such as aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose into sorbitol and fructose. As these sugar products accumulate, the synthesis of nerve cell myoinositol is decreased, affecting nerve conduction. Further, hyperglycemia-induced microangiopathy conducts the reversible

metabolic, motor and sensory nerves, immunologic and ischemic injury of autonomic. It induces low peripheral sensation and compensation fine vasomotor control of the pedal circulation and the nerve innervations of small muscles of the foot. When the nerve gains hurt, the patient is at a high risk of a minor injury without spotting it until it makes an ulcer. The risk of expanding foot ulcers in patients. The sensory loss is increased up to seven-fold, oppose to non-neuropathic patients with diabetes. DM also influences leading to dryness and fissuring of skin, making it prone to infection, the autonomic nervous system. the microcirculation of skin is controlled by the autonomic system. These changes assist in the expansion of gangrene, ulcers, and limb loss. Peripheral neuropathy has also been in Charcot neuroarthropathy (Figure 1).[2,8,17]



**Figure 1.** Common pathway of diabetic foot ulcer occurrence and recurrence [8].

## 7. Vasculopathy

Hyperglycemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial dysfunction is the most serious impairment affecting microcirculation, owing to changes in the proliferation of endothelial cells, thickening of the basement membrane, decreased synthesis of nitric oxide, increased blood viscosity, alterations in microvascular tone and decreased blood flow.[1] Nitric oxide is synthesized by endothelial cells which influence vasodilation and secure the blood vessels from the endogenous wound. Accordingly, in hyperglycemia, perturbation of the physiological properties of nitric oxide usually anticoagulation, regulates the endothelial homeostasis, smooth muscle cell proliferation and antioxidant capacity, leukocyte adhesion. Endothelium-derived vasodilators and nitric oxide decreased. It leads to the propensity for atherosclerosis, constriction of the blood vessels and eventually leading to ischemia. Ischemia also happens, in fact, the attendance of palpable pedal pulses. The microcirculation is also disturbed due to arteriolar-venular shunting, reducing the blood circulation to the area of need. Hyperglycemia in DM also associated with an increase in thromboxane A2 leading to plasma hypercoagulability. Clinically the patient may have signs of vascular insufficiency such as claudication, night pain or rest pain, absent peripheral pulses, thinning of the skin, loss of limb hair, etc.[2]

## 8. Immunopathy

The immune system of a patient with diabetes is much weaker than the healthy people. Thus, foot infection in a patient with diabetes is a limb-threatening and debilitating condition. The hyperglycaemic state causes an elevation of pro-inflammatory cytokines and impairment of polymorphonuclear cell functions like chemotaxis, adherence, phagocytosis and intracellular killing. The immune system is compromised by lowered leukocyte activity, inappropriate inflammatory

response and the disruption of cellular immunity (inhibition of fibroblast proliferation and impairment of the basal layer of keratinocytes, reducing epidermal cell migration).[1] Leukocyte phagocytosis was significantly reduced in patients with poorly controlled diabetes, and improvement of microbiocidal rates was directly correlated with correction of hyperglycemia. Decreased chemotaxis of growth factors and cytokines, coupled with an excess of metalloproteinases, impede normal wound healing by creating a prolonged inflammatory state. Fasting hyperglycemia and the presence of an open wound create a catabolic state. Negative nitrogen balance ensues secondary to insulin deprivation, caused by gluconeogenesis from protein breakdown. This metabolic dysfunction impairs the synthesis of proteins, fibroblasts, and collagen, and further systemic deficiencies are propagated which lead to nutritional compromise. Research indicates impairment of the immune system with serum glucose levels  $\geq 150$  ml/dl. Patients with diabetes tolerate infection poorly and infection adversely affects diabetic control. This repetitive cycle leads to uncontrolled hyperglycemia, further affecting the host's response to infection.[18] High blood glucose is a good medium for the growth of bacteria, mainly aerobic gram-positive cocci like *S. Aureus* and  $\beta$ -hemolytic streptococci but in one research conducted in India, gram-negative aerobes were the common microorganisms in the diabetic foot. Muscles sheaths, tendons, the soft tissues of foot like plantar aponeurosis, and fascia cannot resist infections. Further, some part of the foot are interconnected and could not restrict the dissemination of infection from one to another. The soft tissue infection dissemination to the bones, making osteitis. So an ulcer on the foot can outcome in complications such as gangrene without appropriate and care osteitis/osteomyelitis. [2]

## 9. Mechanical stress

Insensate limbs are inclined to wound which is often neglect. The movements of the foot similar flexion and extension are influenced because of the harm to innervations of the foot muscles. It guides to a transformation of the anatomical structure of the foot and formation of deformities. The deformities create abnormal bone elevated and pressure points impress ulcers. Metatarsal fat pads are stranded reducing the cushioning result of the metatarsal heads and increase the pressure points which guide to callus formations that induce skin damage and ulceration.[2] In people with neuropathy, minor trauma (e.g. from ill-fitting shoes, walking barefoot or an acute injury) can precipitate ulceration of the foot. Loss of sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot. This produces a high pressure in some areas, to which the body responds with thickened skin (callus).[19] Usually, ulcers happen in the plantar of great toe and heel and unfitting shoes (which are the source of trauma) can cause ulcers on the dorsal aspect. Hence neuropathic foot ulcer formation in patients with diabetes has a complex multifactorial aetiopathogenesis wherein areas of high pressure complimented by peripheral neuropathy and associated skin changes lead to ulcer formation.[2]

## 10. Neuroarthropathy

A chronic painless progressive degenerative arthropathy is popular as Charcot neuroarthropathy (CN) resulting from the disruption in sensory innervations of the affected joint. Charcot foot is an insidious, destructive, and progressive pathological condition that affects the foot bones and leads to a deformity that may cause ulcer formation and subsequent disability. The development of Charcot's foot is characterized by subluxation and joint dislocation, osteolysis and bone fragmentation, and soft tissue edema.[20] The demolition of the autonomic nervous system because of DM causes an upgrade in local blood provide and the resting blood flow is higher than in the normal patient. The incidental elevated in blood flow due to calcium to dissolve, leading the osteoclastic activity of the bone and damaging the bone. Another theory is that the repeated small trauma to the insensate joints conducts to fracture and disintegration. The pro-inflammatory cytokines production conducts to uncontrolled osteolysis in CN. The cytokines like tumor necrosis factor- $\alpha$  and interleukin- $1\beta$  increase the expression of receptor activator of nuclear factor- $\kappa$ b (RANKL), which in turn makes maturation of osteoclasts by causing the production of nuclear factor- $\kappa$ b. The hallmark deformity associated with

this condition is a midfoot decay, also known as “rocker-bottom” foot. There might be hallux valgus deformity and loose bodies in the joint cavity. The deformities connected with CN also predispose to recurrent ulcerations.[2]

### 11. Classification

To date, there are many classifications of the diabetic foot. However, the most commonly used classification systems are the Wagner-Ulcer Classification system and the University of Texas Wound Classification.

### 12. Clinical Presentation

About 50% of patients with foot ulcers due to DM present clinical signs of infection. By definition, infection is characterized by the presence of purulent secretions or at least two of the classic signs of inflammation (erythema, hyperemia, edema, or swelling and pain) but these data can be masked by lack of the sensitivity in the patient due to sensory neuropathy or impaired immune response. It is also common that patients with infection are associated with the poor metabolic control. Therefore, we must take into account other aspects of infected ulcers due to diabetes, including lack of granulation tissue, delayed healing or odor. The prevalence of ulcer is highest in the presence of neuropathy, anatomical disorders, structural and environmental factors such as offloading, high-pressure processes on the plantar foot, the forefoot, midfoot, rearfoot and especially the metatarsals heads. These overloads on the limb associated with limited joint mobility makes the plantar fascia to undergo changes, like thickening and shortening that cause a skin fracture cause poor quality of skin in this area (thick, callused, dry, etc) leading their own skin germs to present bacteria into the skin fracture and potency line over time resulting in serious colonization (presence of at least 100,000 bacteria per gram of tissue) and culminating in infection. It's important to consider that pain is not a prominent sign in patients with infected diabetic foot owing to the loss of sensitivity caused by affected short and long fibers (A-beta and A-delta) secondary to hyperglycemia. In the same way, we have to consider a possible infection in any patient with DM who presents a fever, leukocytosis, or recent metabolic uncontrolled.[21,22]

### 13. Conclusion

Diabetic foot is a DM chronic complication which does not suit the “glamour” status of its more illustrious like the cerebrovascular disease, coronary heart disease, retinopathy or nephropathy. In spite of that, it is responsible for an important proportion of morbidity in DM, inducing patient distress and frequently permanent disability. It is necessary to pay attention to this complication when counseling or revising patients with DM. It is a preventable complication by the simple invention. Usual clinical investigation of the feet and related systems make the mainstay of detecting diabetic foot; investigations are only an adjunct to clinical examination. The treatment is usually conservative and a limb-sparing approach is used, along with proper diabetic control. Management of aetiological factors are like vasculopathy, neuropathy, and infection is essential to get good outcomes.

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