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MINIREVIEWS

Management of diabetic foot ulcers and the challenging points: An endocrine view

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Abstract

Diabetic foot ulcers (DFU) are one of the most challenging complications of diabetes. Up to one-third of patients with diabetes mellitus (DM) may suffer from DFUs during their life. DFU is one of the leading causes of morbidity in patients with DM. The treatment period is challenging, and the recurrence rate of DFUs is high. Hence, establishing prevention strategies is the most important point to be emphasized. A multidisciplinary approach is necessary in the prevention and treatment of DFUs. Patients at risk should be identified, and prevention measures should be taken based on the risk category. Once a DFU is formed, the appropriate classification and evidence-based treatment interventions should be executed. Glycemic control, diagnosis and treatment of vascular disease, local wound care, diagnosis, and treatment of infection should be addressed along with the proper evaluation and management of general health status.

Key Words: Diabetic foot; Diabetic foot ulcer; Amputation; Diabetic foot infection

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Core Tip: Diabetes mellitus is a chronic disorder with dramatic complications. Nearly one-third of patients with diabetes may suffer from foot ulcers during their life. A potentially preventable event usually has dramatic results. The prevention and management of diabetic foot ulcers (DFUs) necessitate a multidisciplinary approach. The most important approach is the prevention of the formation of DFU. Prevention measures should be implemented in a timely manner, and adequate treatment interventions should be executed immediately once it is formed.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that has become a global health problem in the last decades[1]. DM has several complications that affect not only life expectancy but also the quality of life[2,3]. Diabetic foot ulcers (DFU) are one of the most challenging complications of DM. Up to one-third of diabetic patients may suffer from DFUs during their life[4,5]. The global prevalence of DFUs is reported at 6.3%, with DFUs being more common in men than women and in type 2 DM than type 1 DM[6]. The recurrence rate of DFUs is also high. The value reaches 40% within 1 year and 65% within 3 years[4]. Hence, studies should focus on establishing prevention strategies against DFU[4,5].

PATHOPHYSIOLOGY AND PREDISPOSING FACTORS

Peripheral artery disease (PAD) and diabetic neuropathy (DNP) are well-known chronic complications of diabetes[7]. Along with immune dysfunction, PAD and DNP are the main pathophysiological factors that predispose to DFUs[8]. DFUs are associated with DM duration, the presence of DNP, and PAD[9]. DNP is present in 80% of patients with DFUs, and it facilitates ulcer formation by causing decreased pain and pressure sensation. DNP also promotes the formation of anatomic deformities, such as prominent plantar metatarsal heads, hammertoes, Charcot foot, *etc.*[4,10]. Patients with diabetes should be assessed for DNP periodically after the diagnosis of type 2 DM and after the fifth year of type 1 DM. Pain, burning, and numbness should be questioned. Small fibers (by pinprick test and temperature sensation), large fibers (by vibration perception and 10 g monofilament test), and protective sensation (by 10 g monofilament test) should be tested. The tests predict the risk of complications besides screening the dysfunction[7,11,12].

Nearly half of the patients with DFUs have PAD, which is significantly associated with the increased risk of adverse limb events[13]. Vascular symptoms, including reduction in effort capacity, leg fatigue, and claudication, should be assessed. All peripheral pulses should be palpated together with an assessment of extremity appearance and warmth to evaluate perfusion[8,13]. Patients should also undergo the ankle-brachial index (ABI) testing as a part of the examination. The normal value of ABI is between 0.9 and 1.3, which is higher than 1.0[13,14]. A high ABI may be measured falsely in the presence of vascular calcifications[13]. Toe-brachial index (TBI) measurement is also recommended, especially in combination with ABI and arterial Doppler study. The diagnosis of PAD is unlikely in the presence of triphasic Doppler waveforms when the TBI is ≥ 0.75, and the ABI is between 0.9-1.3[13]. In addition, disrupted blood flow may be present at the microvascular level despite the intact or well-treated macrovascular component[15]. Dysfunctional signs of blood flow at the microvascular level can be detected by laser Doppler flowmetry[16]. Furthermore, DM causes immunological dysfunctions at the cellular level, leading to poor healing response and susceptibility to infections[8,17].

CLINICAL SIGNIFICANCE

DFUs are a serious healthcare problem globally. A potentially preventable event, such as a minor trauma, usually has dramatic results. DM remains the primary cause of nontraumatic lower-limb loss worldwide[18-20]. DFUs pose a serious financial burden worldwide, and nearly one-third of expenses for DM is estimated to be for DFUs[21-23]. The presence of DFU is associated with the increased risk of mortality in DM, and this association is stronger than the presence of any macrovascular disease alone[3,24]. The five-year survival rate in patients presenting with DFUs is poorer than that associated with the most common cancers[21]. Therefore, the best approach in the management of DFUs is the implementation of preventive measures based on the risk

class[7,10,25].

IDENTIFICATION AND FOLLOW-UP OF PATIENTS AT RISK

DNP, PAD, foot deformity, and medical history of DFU are the most important risk factors for new DFU formation. These factors are the shadows of the coming event, which is DFU if the preventive measures are not applied in time[4,10,26]. Poor glycemic control, chronic kidney disease (especially dialysis), and smoking are also among the risk factors[7,8]. Diabetic patients should be categorized based on the risk of developing DFU. Thus, the risk factors for DFUs must be screened at least annually [7,12]. The risk classification system developed by the International Working Group on the Diabetic Foot (IWGDF) is useful in daily clinical practice (Table 1)[13].

A diabetic patient with very low risk (IWGDF group 0) must be examined annually for DNP and PAD. The patients who have a higher risk (IWGDF group 1-3) should be examined more frequently (Table 1), and preventive measures should be executed (Table 2)[7,13]. Patients who have moderate-to-high risk should wear therapeutic shoes to reduce plantar pressure and the risk of ulceration. Pre-ulcerative lesions, abundant callus, stinging toenails, and fungal infections (tinea pedis, onychomycosis, *etc*.) should be treated properly. Surgical interventions should be performed to fix deformities, if necessary[7,10,13]. The patient's feet with DNP should be inspected every visit, and the patients at risk should be encouraged and educated about self-care and preventive measures[7].

CURRENT EVIDENCE FOR PREVENTION

Several randomized clinical trials (RCT) evaluated the primary prevention strategies of DFUs, but none of them were high-quality research[27]. Conducting RCT to determine the primary prevention strategies and evaluate their efficacy is a considerable challenge, given that numerous patients and a long follow-up period will be required [21]. On the other hand, conducting RCT on the prevention of ulcer recurrence is technically easier because the recurrence rate is high[4,21]. Suitable therapeutic footwear with appropriate pressure distribution prevents recurrence or worsening of plantar foot ulcers, with high-quality evidence[7].

DNP and PAD are the major predisposing factors of DFU development[28,29]. Thus, the neurosensory and vascular systems of the extremities must be protected to prevent or delay the development of DFUs. The onset and progression of diabetic microvascular complications (retinopathy, nephropathy, and neuropathy) can be delayed by intensive glycemic control. This finding has been shown in type 1 DM, but the current evidence in type 2 DM is weak[30-32]. However, no specific therapeutic agent or approach other than glycemic control can modify the progression of microvascular complications[7,10].

PAD is one of the macrovascular complications of diabetes. The benefit of intensive glycemic control on macrovascular complications in diabetics has not been shown in RCTs, but several epidemiological analyses reported a correlation between an increased rate of cardiovascular disease (CVD) and chronic hyperglycemia[33-35]. The benefit of intensive therapy could not be shown in three large RCTs comparing intensive and conventional therapies in terms of cardiovascular benefits in patients with longstanding DM[36,37]. Unlike these studies, in a research investigating the effect of glycemic control on complications in newly diagnosed DM, the benefit of intensive glycemic control on CVD was shown after a 10-year follow-up on the post-interventional period[38]. The management of other CVD risk factors is particularly important in the prevention or delay of PAD and other macrovascular complications in patients with DM. Smoking cessation, effective treatment of hyperlipidemia and hypertension, weight loss, appropriate nutrition, and exercise habits are important points that should be emphasized in every patient with DM. Exercise should be considered with caution if the patient is in the risk group for DFU. Patients in the low- or moderate-risk group should be advised exercises that increase the motion of foot and ankle, relieve pressure, and decrease neuropathic symptoms. Patients in the risk group should avoid long walks, exercises that increase the pressure on the soles of feet, activities with a risk of trauma, and wearing inappropriate shoes[13].

Table 1 International Working Group on the Diabetic Foot risk classification system

Group	Definition	Ulcer risk	Screening
0	No LOPS and no PAD	Very low	Once a year
1	LOPS or PAD	Low	Once every 6-12 mo
2	LOPS + PAD or LOPS + FD or PAD + FD	Moderate	Once every 3-6 mo
3	LOPS or PAD with one or more of the following: (1) History of a foot ulcer; (2) A lower extremity amputation (major or minor); and (3) ESRD	High	Once every 1-3 mo

LOPS: Loss of protective sensation; PAD: Peripheral artery disease; FD: Foot deformity; ESRD: End-stage renal disease.

Table 2 Preventive measures for diabetic foot ulcers

	Preventive measures
1	Avoid smoking
2	Avoid walking barefoot/in socks without shoes/in thin-soled slippers
3	Avoid hot ground and hot sand
4	Inspect both feet and inside the shoes daily
5	Wash the feet daily (carefully dry especially between the toes)
6	Test water temperature before bath
7	Lubricate dry skin and avoid chemicals
8	Cut the toenails straight
9	Do not remove callus
10	Wear snug shoes (customize if feet have deformity)
11	Change the socks daily

CURRENT TECHNOLOGICAL OPPORTUNITIES FOR MONITORING

The recurrence rate of DFUs is also extremely high in patients who are under follow-up in specialized centers. Thus, systems that facilitate recognition of the early signs of DFU formation must be developed. Patients can refer to health care providers early, and preventive and/or therapeutic appropriate strategies can be executed on time[42]. Risky conditions for DFU formation, such as early signs of inflammation and pressure-induced plantar tissue stress by current technological opportunities, can be screened and followed-up[29]. The available technological devices had been invented for this purpose; these devices include instruments for daily monitoring plantar temperature, socks that enable temperature monitoring continuously, socks that monitor plantar pressure, smart insoles to screen sustained plantar pressure, alarm systems that warn patients to wear offloading devices, activity monitoring devices, *etc*[29].

POINTS TO BE CONSIDERED IN DFU MANAGEMENT

DFU is the major cause of nontraumatic lower extremity amputations (LEA), worldwide[20,39]. Once DFU occurs, the management strategies should be implemented without delay. Numerous studies emphasized the importance of a multidisciplinary team approach in the management of these patients[20,40,41]. The multidisciplinary team should focus on four major points; glycemic control, diagnosis and treatment of vascular disease, evaluation and local management of wound, diagnosis, and treatment of infection[41].

Glycemic control

The importance and role of adequate glycemic control for delaying or preventing chronic complications of DM are discussed above. Although RCTs have shown an association between intensive glycemic control before DFU formation and the low risk of LEAs, to our knowledge, the role of glycemia in the management of active DFU has never been studied in RCTs[42,43]. Considering the known negative effect of hyperglycemia on wound healing and immune defense, hyperglycemia may be associated with negative consequences in patients with DFUs[8,17,44]. Several meta-analyses of observational studies addressed this point[43,45,46]. Margolis *et al*[46] published a meta-analysis of five observational studies including DFUs. Glycemic control was not associated with wound healing according to this study. The other two meta-analyses reported that the high fasting plasma glucose and Hba1c levels were associated with a high rate of amputations[43,45].

In addition to the effect of hyperglycemia on the wound healing process, hyperglycemia causes impaired immune functions and decreased response to infections[20,47]. American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend targeting glucose levels between 140-180 mg/dL without causing hypoglycemia in the majority of inpatients[48]. These levels should be aimed at patients with DFUs treated in inpatient setting.

An intercurrent illness (trauma, infection, surgery, *etc.*) causes impaired glycemic control in diabetics and necessitates adjustment of the therapy. Here, DM patients are predisposed to severe hyperglycemia, diabetic ketoacidosis, and nonketotic hyperosmolar state. Patients treated with noninsulin antidiabetics require insulin. ADA and AACE recommend insulin regimens for critically ill and noncritically ill hospitalized patients[48].

Several oral antidiabetics have other properties besides the glucose-lowering effect. For instance, canagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, is associated with an approximately two-fold increased risk of LEA (primarily at the level of toe or metatarsal) in patients with type-2 DM and established CVD (or at risk for CVD) *vs* placebo[49]. On the other hand, in RCTs of empagliflozin and dapagliflozin, the risk of amputation was similar between the treatment and placebo arms [50]. An increased risk of LEAs was reported with canagliflozin, empagliflozin, and dapagliflozin (for toe amputations) in a pharmacovigilance study. This study relied on several LEA cases[51]. Recent meta-analyses found no associations between SGLT-2 inhibitors and increased LEA risk; however, Chang *et al*[53] compared the use of SGLT-2 inhibitors with other oral antidiabetics and reported that SGLT-2 inhibitors may contribute to the increased risk of LEA[49,52]. A study examining systematic reviews, which evaluated the adverse effects of SGLT-2 inhibitors, summarized the scarcity of high-quality systematic reviews on this topic[54]. To our opinion, SGLT-2 inhibitors may increase the risk of LEA in patients with DFU as a group effect. Conflicting data are available regarding this traffic; thus, exercising cautiousness is reasonable.

Vascular disease

The prevalence of PAD among DFU patients reaches 50%. The presence of PAD is significantly related to adverse limb events. All patients with DFU should be examined clinically for PAD. Doppler sonographic study should be performed with a combination ABI and/or TBI test. No single modality has been defined as optimal. Vascular imaging (and revascularization if PAD is present) should always be considered when the ulcer remains unhealed in 4-6 wk despite the appropriate treatment and normal condition (ABI and TBI)[7,13]. The threshold for performing vascular studies should be very low in DFU patients, especially for those who are unresponsive to treatment[55]. Based on the vascular structure and clinical conditions, surgical bypass or endovascular treatment can be applied as a revascularization therapy[15,55].

Local wound management

The first step in the treatment of DFUs is to classify the wound and assess the patient's medical condition. The depth and width of the ulcer, the presence of ischemia, and infection should be evaluated. Classification systems have been developed for DFUs (Table 3). Wound classification helps in the prediction of prognosis, along with determining the type and intensity of treatment[20,56,57]. All infected and nonvitalized tissues should be removed by surgical debridement, and the abscess should be drained, if present[58]. Other debridement methods, such as mechanical, enzymatic, and biological debridement, are available other than surgical procedures[20]. Surgical

Table 3 Classification systems of diabetic foot ulcers

Classifications system	The evaluated parameters
University of Texas System	Depth, infection, ischemia
Wagner	Depth, necrosis
PEDIS	Perfusion, extent, depth, infection, sensation
SINBAD	Site, ischemia, neuropathy bacterial infection, area, depth
Threatened limb classification: WIfI	Wound characteristics, ischemia, foot infection
IWGDF/IDSA system	Clinical manifestations, the severity of infection, PEDIS grade

IWGDF: International Working Group on the Diabetic Foot; IDSA: Infectious Disease Society of America.

debridement is the most effective and preferred method[20,58].

Post-debridement wound care is vital. Further tissue injury should be avoided. Proper wound coverage and dressing are necessary. Negative pressure therapy can be used if the wound is clean. Wound characteristics are determinative of the dressing procedure. Pressure reduction is another important point for wound healing. Several available methods of mechanical offloading (cast walkers, wedge shoes, bed rest, *etc.*) are also applied. Surgical pressure reduction may be needed occasionally[20,56,57].

Management of infection

DFUs are predisposed to infection. The exact diagnosis of infection should be performed correctly the first time to manage the infection in DFUs. The classical manifestations of inflammation (warmth, erythema, tenderness, and swelling), extent of infection, involvement of deep tissues and/or bones, and presence of an abscess and/or fistula tract should be evaluated. The clinician should be acquainted with the clinical findings of necrotizing infections. Systemic manifestations of infection (including findings of systemic inflammatory response syndrome and sepsis) and hemodynamic status should also be assessed carefully along with the wound characteristics[58,59]. The presence of severe infection, extensive gangrene, necrotizing infection, deep abscess, compartment syndrome, and/or limb-threatening ischemia needs immediate consultation with a surgeon[59].

Most diabetic foot infections are polymicrobial. A wound specimen must be obtained for culture if no clinical sign of infection is observed[56]. However, the specimens for culture should always be collected in the presence of infection (especially in moderate-to-severe infection) before antibiotic administration[56,59]. Specimens for culture can be collected by aspiration of the abscess, curettage from the ulcer (after debridement), or biopsy during the surgical procedure (from deep tissue or bone) but not by superficial swab[58,59].

Empiric antimicrobial therapy should be considered in the presence of infection, and the selection of antibiotic should be based on clinical findings and the severity of infection[56,58,59]. An antibiotic regimen that covers gram-positive organisms only is preferable in antibiotic-naive patients with mild infections. In the case of antibiotic treatment in the last several weeks of, severely ischemic limb, or moderate-to-severe infections, the coverage of antibiotic therapy should include commonly isolated gram-negative organisms and anaerobes (in certain conditions) besides gram-positive organisms[59]. The clinical course and culture results should drive antibiotic therapy during follow-up[56,59].

POTENTIAL ADJUNCTIVE THERAPIES

In addition to all these interventions, several adjunctive therapies may help the healing of DFUs [negative pressure wound therapy (vacuum-assisted closure), skin grafts and substitutes, hyperbaric oxygen therapy, shock wave therapy, growth factors, autologous combined leucocyte, platelet, fibrin, and placental derived products][56,60]. No high-quality evidence supports the recommendation of these interventions without concern, and none of these treatments is an alternative to the best standard therapy[60].

CONCLUSION

A DFU is a challenging complication of diabetes that has become a global health problem. The treatment process is troublesome for the patient and healthcare team, and the treatment results are often unsatisfactory, especially in advanced cases. Moreover, the recurrence rate is high despite the healing of ulcer. DFUs are one of the leading causes of morbidity in diabetic patients.

DFUs are potentially preventable. Hence, strict implementation of primary and secondary prevention strategies should be implemented. However, the scarcity of high-quality evidence especially in establishing preventive measures for primary prevention is a challenge.

The multidisciplinary team approach is the cornerstone of the management of DFU. All the team members should be experienced in their field. The evidence-based standard follow-up and treatment algorithms should be applied without delay once an ulcer develops.

Geographic heterogeneity in terms of access to adequate healthcare equipment and experienced healthcare team, poor adherence of the patients, late reference to health care providers, difficulties in achieving adequate perfusion of ulcer, the presence of DNP, the impossibility of restoring sensation, and high recurrence rates are the featured challenging points in the management of DFU.

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