Review Article

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Prevention of Diabetic Foot Ulcer to Safeguard Limbs and Lives of Patients with Diabetes Mellitus: A Mini Review

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Diabetic foot disease has been recognized as a major and serious complication in patients with diabetes mellitus due to the severely disturbed quality of life caused by the disabling severity of this clinical entity. An ulcer on the foot is the most common initial clinical sign of diabetic foot disorder. It has a prevalence of 25% and poses a lifetime risk in diabetic patients. Furthermore, a previous superimposed infection may precede 85% of all non-traumatic lower extremity amputations and up to 70% of the diabetic patients with an ulcer-related amputation may die within 5 years of the procedure. In the absence of prompt diagnosis and early and appropriate management, there could be unavoidable sacrifice of a significant amount of tissue mass or even limb(s) to avoid life-threatening systemic infection or even mortality. The best strategy to minimize the burden caused by diabetic foot ulcers is to prevent their initial occurrence by good and long-term glycemic control, since chronic hyperglycemia is believed to be a critical pathophysiological factor underlying the development and progression of diabetic neuropathies and its presence is associated with a high risk of ulcer formation. Structured educational programs are required for the patients, their families, and caregivers, emphasizing the need for periodic and careful examination of the foot for any unnoticed injury of local tissues and for keeping a watchful eye on the signs or symptoms of any foot deformity or peripheral artery disease.

Key words: diabetes foot ulcer, diabetic peripheral neuropathy, peripheral artery disease

Introduction

Diabetic individuals are at a high risk of developing a variety of complications involving the cardiovascular and nervous systems that may evolve into lower extremity lesions.[1-4] Diabetic neuropathy and/or peripheral artery disease (PAD) are two major pathophysiological changes underlying the development of diabetic foot ulcers (DFUs).[5-7] In patients with diabetic peripheral neuropa-

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thy (DPN), minor trauma caused by a loss of protective sensation (LOPS) can precipitate ulcer formation on the foot.[8,9] PAD, which is generally caused by atherosclerosis, is another critical risk factor contributing to poor and slow wound healing, wound infection, and even loss of a substantial amount of local tissue or amputation of the lower extremity when local circulation is severely obstructed.[10] To prevent the formation of foot ulcer, it would be important to implement multifaceted approaches that encompass the following factors: (1) treating risk factors for ulcer formation (primarily glycemic control), (2) educating the patients, their families, and healthcare professionals to perform periodic and careful inspection of the foot for risk identification, (3) ensuring routine wearing of appropriate footwear and customized therapeutic footwear for offloading in high-risk patients when indicated, and (4) local wound care, diagnosis, and treatment of ischemia when present. These key elements should be considered, addressed comprehensively, and fit into the managed care scheme to prevent the development, exacerbation, and recurrence of DFUs.[11-14]

Epidemiology of diabetic foot ulcers

The estimated lifetime incidence rate of DFUs is between 19% and 34%, with a yearly incidence rate of 2%. Notably, after successful healing of the initial DFU, the recurrence rates are as high as 40% within a year and 65% within 3 years.[6,12] Among diabetic patients who had suffered from lower extremity amputation (LEA), 85% had a history of foot ulceration, which subsequently deteriorated to severe gangrene or infection that was beyond any medical treatment.[15] A systematic review and meta-analysis conducted in different regions reported a global DFU prevalence of 6.3%. Higher rates were observed in men compared to women and in patients with type 2 diabetes mellitus (T2DM) compared to those with type 1 diabetes mellitus (T1DM).[16] Diabetic neuropathy, PAD, foot deformity, and a history of previous DFU or LEA are the risk factors consistently associated with DFU development.[17] Hence, identification and proper management of these factors are paramount to reducing the risk of DFU occurrence. A previous study on the prevalence and trends of diabetic foot complications (DFCs; defined as ulcers, infections, gangrene, and hospitalization for PAD) in Taiwan analyzed the National Health Insurance Research Database data from an 8-year period (2007 to 2014). The results revealed that with a prevalence of approximately 2% per year retained throughout the study period, the absolute number of individuals with DFCs increased by 33.4%, a figure that paralleled the increasing T2DM population. Further analysis revealed that diabetes-associated comorbidities including hypertension, dyslipidemia, and end-stage renal disease had also increased. On the other hand, due to a concomitant increase in vascular interventions (6.2% to 19.5%, $p < 0.001$), the incidence of gangrene at presentation decreased from 14.7% to 11.3% ($p < 0.001$) during this period. Furthermore, the annual incidence of LEAs decreased from 2.85 to 2.06 per 1,000 patients with T2DM ($p = 0.001$), with the major LEA proportion decreasing from 56.2% to 47.4% ($p < 0.001$). The results implied that while the increase in vascular interventions supported the promising values indicating reduced severity of the foot lesions at presentation (such as gangrenous changes), DFCs still represent a sustained major medical problem. Continuous clinical vigilance and rapid, coordinated interdisciplinary care for diabetic foot are still required for diabetic patients.[18]

Pathophysiological mechanisms underlying the development of diabetic foot ulcers

Among these, of the multiple factors predisposing to a higher risk of DFU formation in diabetic patients, neuropathy and PAD are

the most prominent.[19] Current guidelines have defined at-risk patients as diabetic patients who do not have an active foot ulcer, but who have at least LOPS or PAD.[20]

Diabetic neuropathy

Epidemiological studies have found that only neuropathy is encountered in approximately 50% of the cases of diabetic foot disease (DFD).[21] Peripheral sensory neuropathy may lead to an insensitive foot. With a lack of awareness of repeated trauma, it can precipitate into breaking of skin and ulceration of the local tissue.[5,8,9] In addition, thickened skin (callus) may develop in response to mechanical stress, especially over the plantar surface of the forefoot where the tissue is thinner but stiffer. Further increase in loading at the site of the callus leads to a hidden subcutaneous hemorrhage and eventually skin ulceration.[22,23] On the other hand, neuropathy involving the motor nerves has been associated with weakness of the innervated muscles.[24] With time, muscle weakness could be followed by wasting and atrophy, which may cause further alterations in the normal foot dynamics and pressure distribution as well as loss of joint stability with consequent development of foot deformities. Irrespective of the type of foot deformity (equinus or varus deformity, hammer toes, cocked-up toes, or flat foot changes), these changes may lead to an imbalance in pressure distribution, increased shear stress and friction, and ultimately foot ulceration.[25] Elevated dynamic plantar foot pressure significantly increases the risk of foot ulceration. A previous study demonstrated that the presence of local deformity was a prominent factor contributing to the elevated dynamic plantar pressure while measured barefoot.[26] Distinctively, a combination of peripheral sensory (especially proprioception and pain) and autonomic neuropathy may predispose to the development of Charcot foot (Charcot neuropathic osteoarthropathy), a progressive disease affecting the joints, bones, and soft tissues of the foot and ankle.[27]

Peripheral artery disease

PAD alone accounted for 15% of the cases of DFD, whereas lesions were noted to have a combination of neuropathy and vasculopathy in 35% of the cases.[28,29] PAD is generally caused by atherosclerosis. It is a critical risk factor for impaired wound healing and LEA.[10] Notably, patients having ischemic DFU etiology have more severe clinical and ulceration features and worse outcomes than those with neuropathic etiology.[30,31] A large cohort from clinical studies conducted at a multidisciplinary foot care center included 1,151 diabetic patients who were managed for DFUs with percutaneous transluminal angioplasty, reconstructive surgery, or medical treatment alone according to clinical indication. In this cohort, the factors affecting the outcome of primary ulcer healing included the severity of PAD, older age, comorbidities (congestive heart disease and/or renal impairment), and extent of tissue destruction at inclusion. A notable healing rate of 72% without major amputation was observed in surviving patients.[32]

Neuroischemic ulcers

The prevalence of neuroischemic ulcers has been increasing. Patients with these ulcers exhibit better ankle-brachial index (ABI), skin perfusion pressure (SPP), and transcutaneous oxygen pressure ($tcPO_2$) values compared to those with ischemic ulcers. However, symptoms may be obscure or absent due to the obtunded sensation of pain in the presence of neuropathy despite marked ischemia of the local tissue. Neuroischemic ulcers tend to develop at earlier stages of the disease. This may imply a need to apply a higher threshold for SPP and $tcPO_2$ during PAD screening in patients with peripheral neuropathy.[12,33,34]

Regardless of the primary cause of ulceration, persistent walking and loading on the foot impairs healing of the ulcer due to a lack

of awareness of the existing injury. Hence, it is a critical risk factor that should be addressed with constant and purposeful clinical efforts.[35,36]

Risk factors for diabetic foot ulcers

Poor glycemic control

Chronic hyperglycemia causes sensory neuropathy due to accumulation of glycated end-products inside the axons as an irreversible destructive sequela of impaired axonal regeneration that interferes with appropriate target nerve re-innervation and functional repair.[37-39] Impaired nerve conduction causes loss of normal sensation of the limbs and a lack of awareness of potential soft tissue or bone injuries that may result in subsequent breaking of the skin due to impaired first-line defence.[40] Poor wound healing may also be associated with hyperglycemia, which interrupts migration and function of anti-inflammatory cells toward the site of the lesion.[41] Reasonable glycemic control has been shown to help the healing process of DFUs.[42] In the Diabetes Control and Complications Trial, a cohort of T1DM patients who received intensive therapy and had an average glycated hemoglobin (HbA1c) level of 7.2% exhibited a reduced cumulative incidence of diabetic neuropathy by 60% (95% confidence interval [CI] 38 – 74; $p \leq 0.002$) when compared with those who had received conventional treatment and had an average HbA1c level of 9.0%.[43] Achievement and maintenance of better glycemic control is expected to reduce the risk of DFU.

Vascular endothelium exposed to chronic hyperglycemic milieu can also be injured by excessive oxidative stress caused by over-glycation. This process in turn impairs blood flow, micronutrient supply, and oxygenation to the local tissues, a pathology that may delay the healing process of the wound or the ulcer.[44]

Weakened defense mechanism may be followed by local infection, a critical factor that may prolong wound healing.[45,46] If not addressed properly, the local infection may advance to a systemic infection once the general immunity of the patient is compromised. This leads to a life-threatening systemic infection, especially when the original wound is contaminated by one or more resistant strains.[47,48]

Dyslipidemia

Glucose-mediated oxidative stress may cause injury to the peripheral nervous system, leading to eventual death and loss of neurons. Lipid disorders frequently encountered in diabetic patients have also been considered responsible for the development of neuropathy. A previous clinical study assessed the prevalence and risk factors for DPN in youth having T1DM or T2DM for ≥ 5 years who were enrolled in the SEARCH for Diabetes in Youth (SEARCH) study. Altogether, 1,734 patients with T1DM (mean age: 18 ± 4 years, mean diabetes duration: 7.2 ± 1.2 years, and mean HbA1c level: 9.1 ± 1.9%) and 258 patients with T2DM (mean age: 22 ± 3.5 years, mean diabetes duration: 7.9 ± 2 years, and mean HbA1c level: 9.4 ± 2.3%) were assessed using the Michigan Neuropathy Screening Instrument for the presence and severity of DPN. The results showed that in addition to worse glycemic control over time, atherogenic lipid profiles including higher levels of low-density lipoprotein cholesterol (LDL-C), higher levels of triglycerides, and lower levels high-density lipoprotein cholesterol (HDL-C) were identified as risk factors for DPN in patients with T1DM. However, among youth with T2DM, low HDL-C level was noted as a single metabolic risk factor for DPN. The authors concluded that addressing both poor glycemic control and dyslipidemia may prevent or delay debilitating neuropathic complications in young patients with diabetes.[49] Treatment strategies for PAD-associated atherosclerosis are multifaceted, comprising cholesterol reduction, antiplatelet therapy, anticoagulation, peripheral vasodilators, blood pressure management,

exercise therapy, and smoking cessation.[50] Lipid-lowering therapy (primarily statins) in patients with PAD is endorsed by academic society guidelines with a goal of LDL-C < 70 mg/dL.[51]

Joint deformity

The presence of any foot deformity accompanied by other risk factors increases the risk of ulceration. Clawing of the toes is common, leading to increased metatarsal head pressures that may result in skin breakage due to repetitive stress to an area with impaired sensation in neuropathic patients. Other potential risk factors for DFU include Charcot deformities, hallux valgus (bunion), and hallux rigidus (degenerative arthritis of the first metatarsophalangeal joint), which increase the plantar peak pressure (PP) under the medial forefoot. A high body mass index also appears to increase PP under the lateral forefoot.[52,53]

History of diabetic foot ulcer or lower extremity amputation

History of DFU also belongs to a cluster of multiple risk factors leading to LEAs in patients with diabetes. A history of ulcers increases the risk of another ulcer.[54] A review article derived from 19 studies analyzed the incidence rates of ulcer recurrence and reported an estimated recurrence rate of 40% within a year after ulcer healing, approximately 60% within 3 years, and 65% within 5 years.[6] A meta-analysis using data synthesized from 21 studies involved 6,505 participants including 2,006 patients who required an LEA. The results revealed that in addition to the multiple variables identified as risk factors, DFU patients with a previous history of foot ulcers were significantly more prone to have a clinical indication for amputation (odds ratio: 2.48, 95% CI: 2.00 – 3.07, $p < 0.00001$) than those with first-time foot ulcers.[55] A previous study suggested that foot ulcer recurrence implied the persistence of risk factors.[56] Without sustained and effective interventions, persistence of these factors may lead to ulcer progression and even irreversible limb loss.[57]

Risk classification

A well-validated classification and scoring system can help in clinical management as well as outcome auditing in terms of best clinical practice.[58] The International Working Group on the Diabetic Foot (IWGDF) 2019 Risk Stratification System can be applied to identify at-risk feet in diabetic patients (Table 1).[59] In a critical review on the currently available classifications and scoring systems, the authors concluded that the WIfI (*W*ound, *I*schemia, and *f*oot *I*nfection) system for expert assessment and reassessment of peripheral tissue perfusion

Table 1. The IWGDF 2019 Risk Stratification System and corresponding foot screening frequency.

Category	Ulcer risk	Characteristics	Frequency*
0	Very low	No LOPS, No PAD	Once a year
1	Low	LOPS or PAD	Once every 6 – 12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Once every 3 – 6 months
3	High	LOPS or PAD, and one or more of the following: - history of a foot ulcer - a lower extremity amputation (minor or major) - end stage renal disease	Once every 1 – 3 months

* Screening frequency is based on expert opinion, since there is no published evidence to support these intervals. (Adopted and modified from ref. 56).

IWGDF: The International Working Group on the Diabetic Foot; LOPS: loss of protective sensation; PAD: peripheral artery disease.

showed the best scores for prospective use in clinical management. This classification has been shown to predict multiple outcomes pertinent to DFUs including the extent of healing, time required for healing, LEA occurrence, LEA-free survival, need for revascularization, maintenance of ambulatory and independent living status, costs, and mortality.[60,61] On the other hand, based on the concept of adopting a classification system designed for general implementation of variables that contribute to outcomes in different communities, a simple scoring system called the SINBAD (*S*ite, *I*schemia, *N*europathy, *BA*cterial Infection, and *D*epth of the lesions) score has been proven useful in predicting ulcer outcomes (Table 2).[62] A recently published prospective clinical trial that applied the SINBAD system to assess the outcomes in 120 patients with DFUs revealed that this system could help determine treatment protocols and was considered easy to apply in routine practice.[63] Classification of DFUs is of paramount importance in daily practice, since it helps in communication among health professionals, assessment of prognosis, selecting the best treatment strategy, and audit of outcomes across units and populations in clinical care.[64]

Prevention of first-time diabetic foot ulcer

Management of the diabetic foot is multifaceted and requires constant monitoring by healthcare providers as well as by the patients. Educational self-care programs designed for patients and their family members should be cornerstones to avoid ulcer formation. A cross-sectional survey was conducted in 85 patients with T2DM to identify the knowledge, attitudes, and practices for the prevention of diabetic foot. Results from this questionnaire revealed that 80% of the participants showed willingness to engage in self-care. However, less than half (49.4%) of the participants had acquired knowledge regarding hygiene or the possible symptoms to monitor in terms of foot care. The investigators considered it necessary to develop educational strategies to create awareness as an effective preventive approach to avoid DFD.[65] Educational programs administered to healthcare providers are equally important with emphasis on active screening and management of patients who are at risk of foot ulceration.[66]

Educational programs for patients at risk of diabetic foot ulcers

Therapeutic patient education (TPE),[67]

Table 2. The SINBAD system for classifying and scoring foot ulcers

Category	Definition	SINBAD score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischemia	Pedal blood flow intact: at least one pulse palpable	0
	Clinical evidence of reduced pedal blood Flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area	Ulcer < 1 cm^2	0
	Ulcer ≥ 1 cm^2	
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon or deeper	1
Total possible score		6

(Adopted and modified from ref. 59).
SINBAD score: *S*ite, *I*schemia, *N*europathy, *BA*cterial Infection, and *D*epth score.

which has been defined by the World Health Organization, functions as an instrument that helps patients acquire or maintain the knowledge and competence needed to manage a chronic disease in their daily lives. TPE is composed of organized activities related to provision of information, education for learning self-management, and psychosocial support in different situations related to the disease and its treatment. Thus, TPE is regarded as a fundamental factor in patient self-care. Its goal is to help patients and their families develop the tasks and capacity of self-management to prevent complications, improve adherence and collaboration with healthcare teams, and help them maintain or improve their quality of life.[68]

Neurological evaluation

Neurological evaluation can be accomplished by applying the Semmes-Weinstein 10-g monofilament test for the assessment of protective sensation. A positive test result indicates the presence of LOPS. It is confirmed by the inability of the patient to feel the pressure exerted by the monofilament when pressed against the foot with a force strong enough to bend the filament.[69] In addition to the early diagnosis of peripheral neuropathy, the vibration perception threshold can be assessed using a 128-Hz tuning fork. The response is considered abnormal when the patient loses vibratory sensation while the examiner can still perceive it.[70]

Ankle-brachial index

The ABI should be used in patients with symptoms or signs of PAD (such as intermittent claudication). An ABI score of 0.9 – 1.3 generally excludes PAD. However, ankle pressure and ABI score can be falsely elevated due to pedal artery calcification. Other tests such as toe pressure measurements (normal ≥ 30 mmHg) or $tcPO_2$ (normal ≥ 25 mmHg) are useful for assessing the vascular status of the foot. Urgent vascular imaging and revascularization should be considered in DFU patients with ankle pressure < 50 mmHg, toe pressure < 30 mmHg, or $tcPO_2$ < 25 mmHg.[45]

Offloading for the management of foot deformity

"Offloading" in diabetic foot management includes reduction, redistribution, or removal of detrimental forces applied to the foot, since these forces could be major contributing factors to the occurrence, recurrence, chronicity, or deterioration of ulcers.[71] The mainstay of treatment for Charcot foot is immobilization in a total contact cast, which increases the total surface area of contact for the entire lower extremity, distributing pressure away from the foot. Immobilization should continue until lower extremity edema and warmth have resolved and serial radiography has shown evidence of osseous consolidation, which typically occurs after 3 to 4 months, but can take up to 12 months.[72]

Prevention of recurrent diabetic foot ulcers

After healing of a foot ulcer, the risk of recurrence is high. A systematic review involving 49 studies regarding the recurrence of DFUs revealed that the pooled estimate for recurrence rate was 22.1% per person-year (95% CI: 19.0% – 25.2%).[73] This alarmingly high rate of recurrence implies that our efforts should be directed at rapid healing of open wounds as well as maximizing the ulcer-free days to maintain the state of remission.[74] To investigate the characteristics of DFU recurrence, 573 patients with DFUs were recruited and divided into the initial group (395 patients) and the recurrence group (178 patients). Multiple factor logistic regression analysis showed that duration of diabetes, callus formation, vascular intervention, and amputation were independent risk factors for DFU recurrence.[75] To prevent the recurrence of a foot ulcer, home monitoring of foot temperature, pressure-relieving therapeutic footwear, and certain surgical in-

terventions (digital flexor tendon tenotomy for "hammer" and "claw" toes to release the flexor digitorum brevis/longus tendon contraction) have been considered effective strategies.[76,77]

Conclusions

Patients with diabetes mellitus are at a high risk of developing DFUs. DFUs are precipitated by risk factors including chronic hyperglycemia and dyslipidemia, which may lead to diabetic neuropathies and PAD. Neuropathies may result in a loss of protective sensation, atrophy of muscles, or deformity of joints that predispose to the breaking of skin and formation of ulcers. The lesions may advance to non-salvageable loss of local tissues or even amputation of the lower extremities when jeopardized by severe infection and poor circulation of local tissues due to obstructive vasculopathy. Mortality may be unavoidable in extreme cases. To prevent these complications, a multifaceted approach must be implemented, which consists of optimal metabolic control and structured education programs delivered to patients and their families regarding the knowledge and skills required for careful examination of the foot on a regular basis. Healthcare providers from different subspecialties should work in collaboration to provide objective evaluation of the foot for patients. Such collaborative efforts include periodic neurological (sensory and autonomic) and vascular (ABI) assessment for early detection of at-risk foot. When present, the lesions should be carefully managed by referring the patients to a multidisciplinary foot care team to prevent their exacerbation or recurrence, aiming to save the limbs and lives of the patients.

Author Contributions

YM Song initiated the concept, carrying out retrieving and intense reviewing of the references articles cited, drafting and writing of the manuscript. YY-Huang and SC-Chiou contributed substantially to the forming of the manuscript structures and actively involved in the process of manuscript drafting and revision. All the other authors (all certified diabetes educators) had provided valuable opinions in interpretation of the conclusions acquired from the references cited and contributed equally to the successful completion of the manuscript.

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Conflicts of Interest

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