



HEALING THE DIABETIC SOLE: COMPREHENSIVE INSIGHTS AND STRATEGIES FOR DIABETIC FOOT ULCER MANAGEMENT

Diabetology

**Vanukuri
Madhupriya
Reddy***

Pharm-D, Intern Kvsr Siddhartha College Of Pharmaceutical Sciences *Corresponding Author

**Siddineni Siva
Karthik**

III Pharm-D Kvsr Siddhartha College Of Pharmaceutical Sciences

ABSTRACT

Diabetic foot ulcers (DFUs) pose a significant global health concern, stemming from diverse causes such as poorly controlled diabetes, neuropathy, vascular disease, and inadequate foot care. These ulcers, common in individuals with prolonged and poorly managed diabetes, increase the risk of complications, including osteomyelitis and lower extremity amputation. Among the 537 million people with diabetes worldwide, DFUs represent a substantial and burdensome complication. Complications such as neuropathy, retinopathy, and nephropathy contribute to the chronic nature of diabetes, with DFUs exhibiting a recurrence rate exceeding 50% within three years. Addressing factors like HbA1c control, foot injuries, and comorbidities is crucial for mitigating the prevalence and impact of DFUs in both type 1 and type 2 diabetes

KEYWORDS

Diabetic foot ulcer, Vascular disease, ulcers

INTRODUCTION:

The term "diabetic foot ulcer" (DFU) lacks specificity as it merely denotes a skin break in the foot of a diabetic person who does not promptly heal, without specifying its type. The underlying causes for this skin break are diverse, and once the ulcer has formed, numerous factors hinder its timely healing. Diabetic foot ulcers frequently occur in individuals with poorly controlled diabetes mellitus, often stemming from inadequate glycemic control, neuropathy, peripheral vascular disease, or insufficient foot care. These ulcers commonly develop in regions of the foot exposed to repetitive trauma and pressure, serving as a significant risk factor for osteomyelitis of the foot and the subsequent need for lower extremity amputation.¹ Diabetic foot ulcers (DFU) represent a prevalent and severe outcome of prolonged and inadequately controlled diabetes. Among the approximately 537 million individuals globally living with diabetes, DFUs are a significant and burdensome complication.² The chronic complications of diabetes differ based on the diabetes type, duration since onset, and the level of metabolic control. Among these, the most common are neuropathy (25%), retinopathy (32%), and nephropathy (23%).³ The recurrence rate for diabetic foot ulcers (DFUs) is estimated to exceed 50% within three years.⁴ These complications pose a growing public health concern and stand as primary contributors to hospital admissions, amputations, and mortality among individuals with diabetes.⁵ DFU arises due to inadequate control of HbA1c levels, foot injuries, mechanical pressures, obesity, overweight, tobacco use, prolonged duration of diabetes, and advancing age.⁶⁻¹¹ Additionally, diabetic neuropathy, vasculopathy, ischemia, and neuropathy are recognized as contributing factors to the development of DFUs.^{12,13} Foot complications are prevalent in both type 1 and type 2 diabetes, with a projected lifetime risk for patients developing a foot ulcer reaching as high as 30%.^{14,15}

Epidemiology:

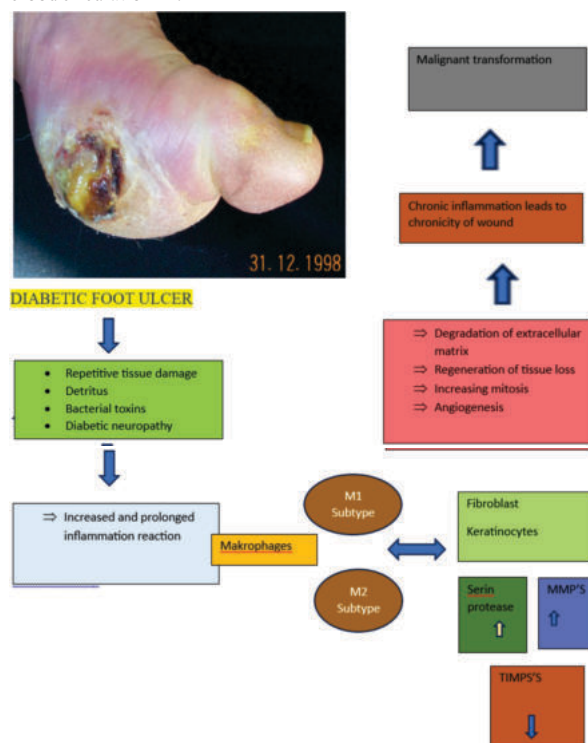
The global annual occurrence of diabetic foot ulcers ranges from 9.1 to 26.1 million cases.¹⁶ Approximately 15 to 25% of individuals with diabetes mellitus are expected to experience a diabetic foot ulcer at some point in their lives.¹⁷

Pathophysiology:

The pathophysiology of diabetic foot ulcers encompasses neuropathic, vascular, and immune system factors, all of which are fundamentally linked to the hyperglycemic condition associated with diabetes.^{18,19} Elevated blood sugar levels induce oxidative stress on nerve cells, resulting in the development of neuropathy.¹⁸ Diabetic ulcer progression typically unfolds in three stages—initially, a callus forms, a consequence of neuropathy.

Traditional Chinese Medicine (TCM) is characterized by its multicomponent nature, addressing various targets and producing multiple effects. From a TCM perspective, the approach to healing

involves restoring the balance of yin and yang, regulating the flow of 'chi' (energy), and enhancing local blood circulation. According to the TCM system, the treatment of Diabetic Foot Ulcers (DFU) should prioritize the improvement and regulation of qi (vital energy), nourishment of yin (body fluids and substances), resolution of dampness, enhancement of spleen function, and activation of stagnant blood circulation.^{19,20}



Normalization Achieved Post-application:

In a preliminary investigation into the impact of Hongyou ointment and Shengji powder, it was observed that refractory wounds exhibit abnormal expression of β -catenin, along with elevated levels of c-myc and K6. Following the administration of the mentioned formulation, these aberrant expressions were effectively downregulated to normal levels.²¹

Potent Antibacterial Action:

While data on the specific effects of individual herbal products in the healing of Diabetic Foot Ulcers (DFU) is limited, in vitro experiments

indicate that extracts from Phellodendri Cortex, also known as Huangbai, exhibit antimicrobial properties against various bacteria, including *Pseudomonas*, *Staphylococcus aureus* (MRSA), *Pneumococcus*, *C. diphtheriae*, *Streptococcus*, and others²²⁻²⁴

Local Coverings:

Dressings play a crucial role in treating Diabetic Foot Ulcers (DFU). Ideally, effective dressings should alleviate symptoms, shield DFU wounds, and facilitate the healing process. A suitable wound dressing should (i) support tissue reconstruction through thermal insulation, gas exchange, enhanced drainage, and debris removal; (ii) demonstrate biocompatibility, avoiding allergic or immune reactions; (iii) prevent secondary wound infections; and (iv) allow easy removal without causing trauma²⁵. Given the diverse nature of wounds and variations in each stage of the healing process, no universal dressing exists that fulfills all requirements for treating Diabetic Foot Ulcers (DFU) across all cases. Various dressing types possess unique characteristics.

Properly selecting and applying dressings enhances the DFU healing rate, subsequently decreasing hospitalization, shortening the healing period, and lowering the overall cost of DFU treatment²⁶.

Decompression Mechanism:

The predominant route to Diabetic Foot Ulcers (DFUs) involves subjecting the insensate foot to excessive mechanical pressure. Elevated mechanical stress can induce inflammation, contribute to the development of DFUs, and extend the healing period, thereby elevating the risks of infection, hospitalization, and amputation. A pivotal objective is to mitigate excessive mechanical stress through offloading interventions, a crucial prerequisite for fostering healing outcomes and averting ulceration.²⁷

This procedure entails diminishing the load on afflicted foot areas by redistributing excess pressure to alternate regions. Methods such as bed rest, wheelchairs, gait-assisting crutches, surgical decompression, total contact casts (TCCs), removable cast walkers (RCWs), and offloading shoes are widely employed. Substantial evidence endorses the preference for non-removable knee-high offloading devices, whether TCCs or non-removable walkers, as the primary choice for offloading interventions in healing plantar neuropathic forefoot and midfoot ulcers²⁷.

CONCLUSION:

In conclusion, diabetic foot ulcers (DFUs) present a multifaceted challenge, closely linked to inadequate glycemic control, neuropathy, vascular complications, and other contributory factors. These ulcers, prevalent among individuals with prolonged and poorly managed diabetes, significantly elevate the risk of severe complications, including osteomyelitis and lower extremity amputation. The global prevalence of DFUs underscores the urgent need for comprehensive management strategies that address not only the ulcer itself but also the underlying causes and associated complications. Emphasizing preventive measures, early intervention, and a multidisciplinary approach involving glycemic control, foot care, and vascular health is essential for reducing the substantial burden imposed by DFUs on individuals with diabetes and the healthcare system.

REFERENCES:

- Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. *N Engl J Med*. 2018 Jan 18;378(3):302-303. [PubMed] [Reference list]
- International Diabetes Federation. The Diabetic Foot. Brussels, Belgium, International Diabetes Federation, 2020. Accessed 1 August 2022. Available from <https://www.idf.org/our-activities/care-prevention/diabetic-foot.html>
- Goday, A. Epidemiology of diabetes and its non-coronary complications. *Rev. Esp. Cardiol*. 2002; 55, 657–670. [CrossRef]
- Dubsky, M.; Jirkovska, A.; Bem, R.; Fejfarova, V.; Skibova, J.; Schaper, N.C.; Lipsky, B.A. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. *Int. Wound J*. 2013, 10, 555–561. [CrossRef]
- Buowari, O.Y. Diabetes Mellitus in Developing Countries and Case Series, in *Diabetes Mellitus—Insights and Perspectives*; Ogunlaju, O.O., Ed.; IntechOpen: London, UK, 2013; p. 19.
- Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med*. 2017;49(2):106–116. doi:10.1080/07853890.2016.1231932
- Meidani M, Khorvash F, Rajabpourmikfah MR. The relationship between controlling HbA1C and infected diabetic foot ulcer. *J Isfahan Med Sch*. 2012;30.
- Shahi SK, Kumar A, Kumar S, Singh SK. Prevalence of diabetic foot ulcer and associated risk factors in diabetic patients from North India. *J Diabetic Foot Complications*. 2012;4(3):83–91.
- Mariam TG, Alemayehu A, Tesfaye E, et al. Prevalence of diabetic foot ulcer and associated factors among adult diabetic patients who attend the diabetic follow-up clinic at the University of Gondar Referral Hospital, North West Ethiopia, 2016: institutional-Based Cross-Sectional Study. *J Diabetes Res*. 2017;2017.
- Bakri FG, Allan AH, Khader YS, Younes NA, Ajlouni KM. Prevalence of diabetic foot

- ulcer and its associated risk factors among diabetic patients in Jordan. *Jordan Med J*. 2012;171(785):1–16.
- Taghipour M, Abi Kordadeh E, Eslami M. Review of biomechanical parameters of diabetic foot ulcers. *Razi J Med Sci*. 2016;23(144):51–67.
- Ochoa-Gonzalez F, Cervantes-Villagrana AR, Fernandez-Ruiz JC, et al. Metformin induces cell cycle arrest, reduced proliferation, wound healing impairment in vivo and is associated to clinical outcomes in diabetic foot ulcer patients. *PLoS One*. 2016;11:3.
- Assaad-Khalil S, Zaki A, Rehim AA, et al. Prevalence of diabetic foot disorders and related risk factors among Egyptian subjects with diabetes. *Prim Care Diabetes*. 2015;9(4):297–303. doi:10.1016/j.pcd.2014.10.010
- Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017; 376: 2367e75.
- Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current challenges and opportunities in the prevention and management of diabetic foot ulcers. *Diabetes Care*. 2018; 41: 645e52.
- Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med*. 2017 Jun 15;376(24):2367–2375. [PubMed] [Reference list]
- Clayton W Jr, Elasy TA. A review of the pathophysiology, classification and treatment of foot ulcers in diabetic patients. *Clinical Diabetes*. 2009;27(2):52–58.
- Wolf G. New insights into the pathophysiology of diabetic nephropathy: from hemodynamics to molecular pathology. *Eur J Clin Invest*. 2004;34(12):785–796.
- Xie XS, Wang YJ, Zuo C, Fan JM, Li XJ. A case report of an effective treatment for diabetic foot ulcers with integration of traditional Chinese medicine and Western medicine. *J Diabetes Complications*. 2009;23:360–364. [PubMed] [Google Scholar]
- Li FL, Wang YF, Li X, Li F, Xu R, Chen J, Geng L, Li B. Characteristics and clinical managements of chronic skin ulcers based on traditional chinese medicine. *Evid Based Complement Alternat Med*. 2012;2012:930192. [PMC free article] [PubMed] [Google Scholar]
- Li FL, Deng H, Wang HW, Xu R, Chen J, Wang YF, Li X, Fan B, Li B. Effects of external application of Chinese medicine on diabetic ulcers and the expressions of β -catenin, c-myc and K6. *Chin J Integr Med*. 2011;17:261–266. [PubMed] [Google Scholar] [Ref list]
- Liu Y, Li Y, Du Y, Huang T, Zhu C. Multicenter Clinical Trials Analyzing Efficacy and Safety of Topical Cortex Phellodendri Compound Fluid in Treatment of Diabetic Foot Ulcers. *Med Sci Monit*. 2020;26:e923424. [PMC free article] [PubMed] [Google Scholar] [Ref list]
- Morita Y, Nakashima K, Nishino K, Kotani K, Tomida J, Inoue M, Kawamura Y. Berberine Is a Novel Type Efflux Inhibitor Which Attenuates the MexXY-Mediated Aminoglycoside Resistance in *Pseudomonas aeruginosa*. *Front Microbiol*. 2016;7:1223. [PMC free article] [PubMed] [Google Scholar]
- Sun Y, Lenon GB, Yang AWH. Phellodendri Cortex: A Phytochemical, Pharmacological, and Pharmacokinetic Review. *Evid Based Complement Alternat Med*. 2019;2019:7621929. [PMC free article] [PubMed] [Google Scholar]
- Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review. *Acta Biomater* (2013) 9:7. doi: 10.1016/j.actbio.2013.03.033 [PubMed] [CrossRef] [Google Scholar] [Ref list]
- Saco M, Howe N, Nathoo R, Cherpelis B. Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success. *Dermatol Online J* (2016), 22(8):13030/qt7ph5v17z. [PubMed] [Google Scholar] [Ref list]
- Wang X, Yuan CX, Xu B, Yu Z. Diabetic foot ulcers: Classification, risk factors and management. *World J Diabetes* (2022) 13(12):1049–65. doi: 10.4239/wjcd.v13.i12.1049 [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]