The Diabetic Foot Ulcer

Subjects: Infectious Diseases

Contributor: Prakhar Srivastava , Tesalonika Sondak , Karthikeyan Sivashanmugam , Kwang-sun Kim

The term “neuropathy” in diabetes is a generic term that refers to the loss of sensation and steadiness of the distal limb. The loss of sensation affects peripheral blood movement. Therefore, dysregulating the protective sensation leads to systemic inflammatory status of diabetic foot ulcers (DFUs). Diabetic foot ulcers (DFUs) are characterized by a lack of angiogenesis and distal limb diabetic neuropathy.

diabetic foot ulcer biofilm acute chronic

1. Introduction

The term “neuropathy” in diabetes is a generic term that refers to the loss of sensation and steadiness of the distal limb. The loss of sensation affects peripheral blood movement. Therefore, dysregulating the protective sensation leads to systemic inflammatory status of diabetic foot ulcers (DFUs) [1]. Characterizing the type of wound—which considers various factors such as the length of the wound, the size of the ulcer, and its location—is a crucial step in the evaluation of DFUs. These parameters primarily indicate whether the ulcer is acute or chronic in nature [2]. From the acute to the gangrene stages, DFUs express differently. The acute stage begins with a recurring loss of sensation and subcutaneous hemorrhage of the lesion, which usually goes unnoticed and results in foot deformity. It normally heals in three weeks, but improper wound management in the acute stage leads to a chronic or infectious stage with inflammatory dysregulation [3].

However, due to the broad pathophysiology of DFU infection, relying on any single therapy [4] causes local inflammation, bleeding, and a high increase in blood oxygen levels. To overcome such limitations, therapies targeting immune cells using fibroblasts, stem cells, grafts, monoclonal antibodies, and bioactive molecules have been recently developed. However, these therapies have some limitations. A short half-life, the need for repeated administration, high costs of production, short-term bioactivity, insufficient data on large populations, limited downstream processing, renal clearance, and ineffectiveness against polymicrobial infections are all issues that must be addressed [5].

Gut immunological homeostasis, which is maintained by the interaction among intestinal microflora, is crucial in controlling the host’s inflammatory response. The gut microbiota influences various parts of the human body, including the brain, liver, and skin. Concerning DFU infection, commensal microbes (*Staphylococcus epidermidis*, *Propionibacterium*, and *Cutibacterium* species) on human skin have direct coordination with the gut microbiota and govern chronic responses during skin–pathogen contact [6]. Among gut microbiota, probiotics have been used to treat a variety of health issues since long ago and have also shown promising results as immunomodulators during

chronic illness [7]. Probiotics already have several advantages, including non-toxicity, user-friendliness, strong immunity, a longer half-life, an easy route of administration, and simple downstreaming [8]. However, questions still remain about the use of probiotics as a DFU therapeutic. Constant remodeling of probiotics through encapsulation or nanoformulation using prebiotics and synbiotics, biogenic nanoparticles (NPs), and extracellular vesicle (EVs) originating from probiotics can open new avenues in the field of DFU management. These strategies are still unexplored.

2. The Diabetic Foot Ulcer: A Long-Lasting Foot Deformity

The DFU, one of the major complications of diabetes, affects 25 to 30% of people during their lifetime. Among them, 20% undergo lower limb amputation with an annual mortality rate of 11% for DFUs and 22% for amputees [9]. Every 20 to 30 s, a lower limb gets amputated, with DFUs accounting for 85–95% of the cases [10]. Patients with high blood glucose levels exhibited severe pathological conditions such as tissue hypoxia, leading to inadequate blood supply to the vascular endothelial cells [11]. The prognosis involves a localized injury to the distal portion of the ankle, which goes unnoticed due to inefficient sensory response, peripheral neuropathy, and vascular lesions. The lesion paves the way for opportunistic pathogens that increase the chances of tissue hypoxia by reducing the process of angiogenesis and endothelial revascularization, which in turn delay the wound-healing process. This delay in the wound-healing process results in the chronic stages of DFUs and the formation of gangrene [12][13]. The process from neuropathy to gangrene follows a gradual infectious route, which leads to a high microbial bioburden [14] and delays the wound-healing process at chronic stages due to the formation of microbial communities known as biofilms. High blood glucose levels increase the concentration of proteins and carbohydrates, which form the basic core for persistent infections. About 40 to 80% of diabetic patients develop recurrent infections, and between 20 to 25% develop deep infections with osteomyelitis [15]. To select the appropriate treatment course and manage care for DFU patients, several classification systems have been developed to elucidate the characteristics of DFUs and the severity of infections as described below.

2.1. Evaluation and Classification of DFU Extent

The systematic evaluation of DFUs defines the constant prognosis of foot ulcers. Health professionals determine the etiology of the foot and verify the extent of lesions that involve acute Charcot foot or chronic ischemic foot [16]. Various classification systems have been developed to describe ulcer characteristics and its lower limb extremities.

2.1.1. Meggitt–Wagner (MW) Classification System

Developed in the 1970s, this system comprises six ulcer grades that range from 0 to 5. This system assesses the pro-ulcerative stage, superficial infection, subcutaneous infection, deep ulcer in tendons, forefoot gangrene, and whole-foot gangrene (50% foot infection) [17]. This system is simple and widely accepted for predicting lower extremity amputation. However, this system is not recommended for use in assessments of DFUs because it does not adequately address all DFU subtypes and the spectrum of infections. The major limitations of this system are the infection rate and tissue viability [18].

2.1.2. University of Texas (UT) Classification

This system is a modified version of the MW classification that has also been effective in predicting lower extremity amputation. Moreover, this system overcomes all of the shortcomings of MW, especially the depth of lesion and infection rate [19]. This system uses four grades (0 to 3; depth) and four stages (A–D; severity of wound) to classify DFUs by marking the presence of infection, ischemia, or both [20]. This system helps predict the infection rate and the rate of amputation and is used in practice; however, it is ineffective in determining the degree of neuropathy and microbial load differentiation.

2.1.3. Perfusion, Extent, Depth, Infection, and Sensation (PEDIS)

This system was developed in 2003 by International Working group of Diabetic Foot (IWGDF) solely for determining the rate of infection. It includes four categories. The first is uninfected or pro-ulcerative (the same as MW and UT); the second involves signs of infection, erythema, or colitis. The last two stages involve the severity of the infection and its related circumstances such as moderate to severe infection and systemic toxicity involving fever, chills, hypertension, and cardiovascular disorders [21]. It is a complex system that does not truly define the ulcer types but has an advantage in terms of choosing empirical antibiotic therapy against chronic infection.

2.1.4. Saint Elian Wound Score System (SEWSS)

This is an advanced version of the PEDIS system. This system uses three grades (I to III) based on 10 factors in the following categories: location, topographic aspects, the number of affected zones, ischemia, infection, edema, neuropathy, depth, area, and wound-healing phase. The total score is 6 to 30 points, and the score can switch to a grade. It is an advantageous system compared to others and can efficiently detect the outcome of DFUs (minor amputation and wound healing), but it is time-consuming [22].

2.1.5. Site, Ischemia, Neuropathy, Bacterial Infection, Area, and Depth (SINBAD)

This is a versatile and rapid system that uses five clinical features (site of infection, ischemia condition, neuropathy, bacterial infection, and depth), which are graded as either present (0) or absent (1). This system is primarily used in various rural regions where DFU occurrence is very prominent and does not require any medical setup for evaluation. SINBAD generally provides a high degree of versatility and also helps to differentiate between the acute and chronic conditions in the context of validating research and consistent results [23].

References

1. Feldman, E.L.; Callaghan, B.C.; Pop-Busui, R.; Zochodne, D.W.; Wright, D.E.; Bennett, D.L.; Bril, V.; Russell, J.W.; Viswanathan, V. Diabetic neuropathy. Nat. Rev. Dis. Primers 2019, 5, 41.
2. Ince, P.; Abbas, Z.G.; Lutale, J.K.; Basit, A.; Ali, S.M.; Chohan, F.; Morbach, S.; Mollenberg, J.; Game, F.L.; Jeffcoate, W.J. Use of the SINBAD classification system and score in comparing

outcome of foot ulcer management on three continents. Diabetes Care 2008, 31, 964–967.

3. Shi, L.; Wei, H.; Zhang, T.; Li, Z.; Chi, X.; Liu, D.; Chang, D.; Zhang, Y.; Wang, X.; Zhao, Q. A potent weighted risk model for evaluating the occurrence and severity of diabetic foot ulcers. Diabetol. Metab. Syndr 2021, 13, 92.
4. Karri, V.V.; Kuppusamy, G.; Talluri, S.V.; Yamjala, K.; Mannemala, S.S.; Malayandi, R. Current and emerging therapies in the management of diabetic foot ulcers. Curr. Med. Res. Opin. 2016, 32, 519–542.
5. Jodheea-Jutton, A.; Hindocha, S.; Bhaw-Luximon, A. Health economics of diabetic foot ulcer and recent trends to accelerate treatment. Foot 2022, 52, 101909.
6. Coates, M.; Lee, M.J.; Norton, D.; MacLeod, A.S. The Skin and Intestinal Microbiota and Their Specific Innate Immune Systems. Front. Immunol. 2019, 10, 2950.
7. Kawai, K.; Kamochi, R.; Oiki, S.; Murata, K.; Hashimoto, W. Probiotics in human gut microbiota can degrade host glycosaminoglycans. Sci. Rep. 2018, 8, 10674.
8. Zuo, F.; Marcotte, H. Advancing mechanistic understanding and bioengineering of probiotic lactobacilli and bifidobacteria by genome editing. Curr. Opin. Biotechnol. 2021, 70, 75–82.
9. Jiang, M.; Gan, F.; Gan, M.; Deng, H.; Chen, X.; Yuan, X.; Huang, D.; Liu, S.; Qin, B.; Wei, Y.; et al. Predicting the Risk of Diabetic Foot Ulcers From Diabetics With Dysmetabolism: A Retrospective Clinical Trial. Front Endocrinol. 2022, 13, 929864.
10. Armstrong, D.G.; Boulton, A.J.M.; Bus, S.A. Diabetic Foot Ulcers and Their Recurrence. N. Engl. J. Med. 2017, 376, 2367–2375.
11. Okonkwo, U.A.; Chen, L.; Ma, D.; Haywood, V.A.; Barakat, M.; Urao, N.; DiPietro, L.A. Compromised angiogenesis and vascular Integrity in impaired diabetic wound healing. PLoS ONE 2020, 15, e0231962.
12. Morbach, S.; Furchert, H.; Groblinghoff, U.; Hoffmeier, H.; Kersten, K.; Klauke, G.T.; Klemp, U.; Roden, T.; Icks, A.; Haastert, B.; et al. Long-term prognosis of diabetic foot patients and their limbs: Amputation and death over the course of a decade. Diabetes Care 2012, 35, 2021–2027.
13. Ndosi, M.; Wright-Hughes, A.; Brown, S.; Backhouse, M.; Lipsky, B.A.; Bhogal, M.; Reynolds, C.; Vowden, P.; Jude, E.B.; Nixon, J.; et al. Prognosis of the infected diabetic foot ulcer: A 12-month prospective observational study. Diabet. Med. 2018, 35, 78–88.
14. Yan, X.; Song, J.F.; Zhang, L.; Li, X. Analysis of risk factors for multidrug-resistant organisms in diabetic foot infection. BMC Endocr. Disord. 2022, 22, 46.
15. Ibrahim, A.; Berkache, M.; Morency-Potvin, P.; Juneau, D.; Koenig, M.; Bourduas, K.; Freire, V. Diabetic foot infections: How to investigate more efficiently? A retrospective study in a quaternary university center. Insights Imaging 2022, 13, 88.

16. Game, F. Classification of diabetic foot ulcers. Diabetes Metab. Res. Rev. 2016, 32 (Suppl. 1), 186–194.
17. Santema, T.B.; Lenselink, E.A.; Balm, R.; Ubbink, D.T. Comparing the Meggitt-Wagner and the University of Texas wound classification systems for diabetic foot ulcers: Inter-observer analyses. Int. Wound J. 2016, 13, 1137–1141.
18. Karthikesalingam, A.; Holt, P.J.; Moxey, P.; Jones, K.G.; Thompson, M.M.; Hinchliffe, R.J. A systematic review of scoring systems for diabetic foot ulcers. Diabet. Med. 2010, 27, 544–549.
19. Oyibo, S.O.; Jude, E.B.; Tarawneh, I.; Nguyen, H.C.; Armstrong, D.G.; Harkless, L.B.; Boulton, A.J.M. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet. Med. 2001, 18, 8.
20. Bravo-Molina, A.; Linares-Palomino, J.P.; Vera-Arroyo, B.; Salmeron-Febres, L.M.; Ros-Die, E. Inter-observer agreement of the Wagner, University of Texas and PEDIS classification systems for the diabetic foot syndrome. Foot Ankle Surg. 2018, 24, 60–64.
21. Forsythe, R.O.; Ozdemir, B.A.; Chemla, E.S.; Jones, K.G.; Hinchliffe, R.J. Interobserver Reliability of Three Validated Scoring Systems in the Assessment of Diabetic Foot Ulcers. Int. J. Low Extrem. Wounds 2016, 15, 213–219.
22. Huang, Y.; Xie, T.; Cao, Y.; Wu, M.; Yu, L.; Lu, S.; Xu, G.; Hu, J.; Ruan, H. Comparison of two classification systems in predicting the outcome of diabetic foot ulcers: The Wagner grade and the Saint Elian Wound score systems. Wound Repair Regen 2015, 23, 379–385.
23. Monteiro-Soares, M.; Russell, D.; Boyko, E.J.; Jeffcoate, W.J.; Mills, J.L.; Morbach, S.; Game, F. IWGDF Guidelines on the Classification of Diabetic Foot Ulcers. Diabetes Metab. Res. Rev. 2019, 36 (Suppl. 1), e3273.