International Journal of Research in Medical Sciences
Panchakshari MK et al. Int J Res Med Sci. 2022 Nov;10(11):2717-2721
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20222890

Review Article

Pathogenesis, diagnosis and management of diabetic foot ulcers: a systematic review

Madhuri K. Panchakshari[1], Nilesh J. Patel[2]*, Nimesh B. Thakkar[3], Kenil Kirit Patel[4]

[1]Department of Pharmacology, Saraswati Institute of Pharmaceutical Sciences, Gandhinagar, Gujarat, India
[2]Department of Pharmacology, S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, Gujarat, India
[3]Department of General Surgery, GMERS Medical College, Gandhinagar, Gujarat, India
[4]GMERS Medical College, Gandhinagar, Gujarat, India

Received: 02 September 2022
Accepted: 01 October 2022

***Correspondence:**
Dr. Nilesh J. Patel,
E-mail: Nileshcology127@gmail.com

ABSTRACT

Diabetic foot ulcers lead to substantial morbidity and impair quality of life with high treatment costs and enormous economic losses. Diabetic foot ulcers readily become chronic; all too often these wounds do not heal primarily. Treatment of chronic wounds should be essentially directed against the main etiologic factors responsible for the wound. There are different treatment approaches for wound healing in diabetic foot ulcers. If treatment is based on the pathological cause, it may give better results and it must be cost effective too. Hydrogel dressing, platelet rich plasma, placenta extract gel, vacuum dressing are newer modalities in diabetic foot management.

Keywords: Diabetic foot, Amputation, Conventional dressing, PRP, Placenta extract, Vacuum dressing, Hydrogel

INTRODUCTION

The diabetic foot ulcer is a very severe and common complication in patients with diabetes mellitus with a cumulative lifetime incidence of up to 25 percent.[1] As diabetes is a very common disease in many parts of the world makes diabetic foot ulcers a major and increasing public-health problem. Foot ulcers lead to substantial morbidity and impair quality of life with high treatment costs and enormous economic losses.[2] Diabetic foot ulcers readily become chronic; all too often these wounds do not heal primarily. Treatment of chronic wounds should be essentially directed against the main etiologic factors responsible for the wound.[3,4]

Diabetic foot ulcers are an injury to all layers of skin, necrosis or gangrene that usually occur on the soles of the feet, as a result of peripheral neuropathy or peripheral arterial disease in diabetes mellitus (DM) patients.[5-7]

Once an ulcer has developed and became chronic, there is an increased risk of wound progression that may ultimately lead to amputation; diabetic ulceration has been shown to precede amputation in up to 85% of cases. At least 40% of amputations in diabetic patients can be prevented with a team approach to wound care.[8,9] There are different treatment approaches for wound healing in diabetic foot ulcers. If treatment is based on the pathological cause it may give better results and it must be cost effective also.

Causes and pathogenesis of diabetic ulceration

The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease. More than 60% of diabetic foot ulcers are the result of underlying neuropathy.[10,11] As neuropathy increases, the foot loses its natural ability to moisturize the overlying skin and becomes dry and increasingly

susceptible to tears and the subsequent development of infection. The loss of sensation as a part of peripheral neuropathy exacerbates the development of ulcerations.[9]

Peripheral arterial disease (PAD) is a contributing factor to the development of foot ulcers in up to 50% of cases.[12,13] Endothelial cell dysfunction and smooth cell abnormalities develop in peripheral arteries as a consequence of the persistent hyperglycaemic state.[14] There is a resultant decrease in endothelium-derived vasodilators leading to constriction.

Diabetic ulcer is a chronic wound healing process. The physiological process of wound healing is traditionally divided into four phases: haemostasis, inflammation, proliferation and maturation or remodelling. These phases are orchestrated by a subtle interplay of cellular and humoral factors.[15]

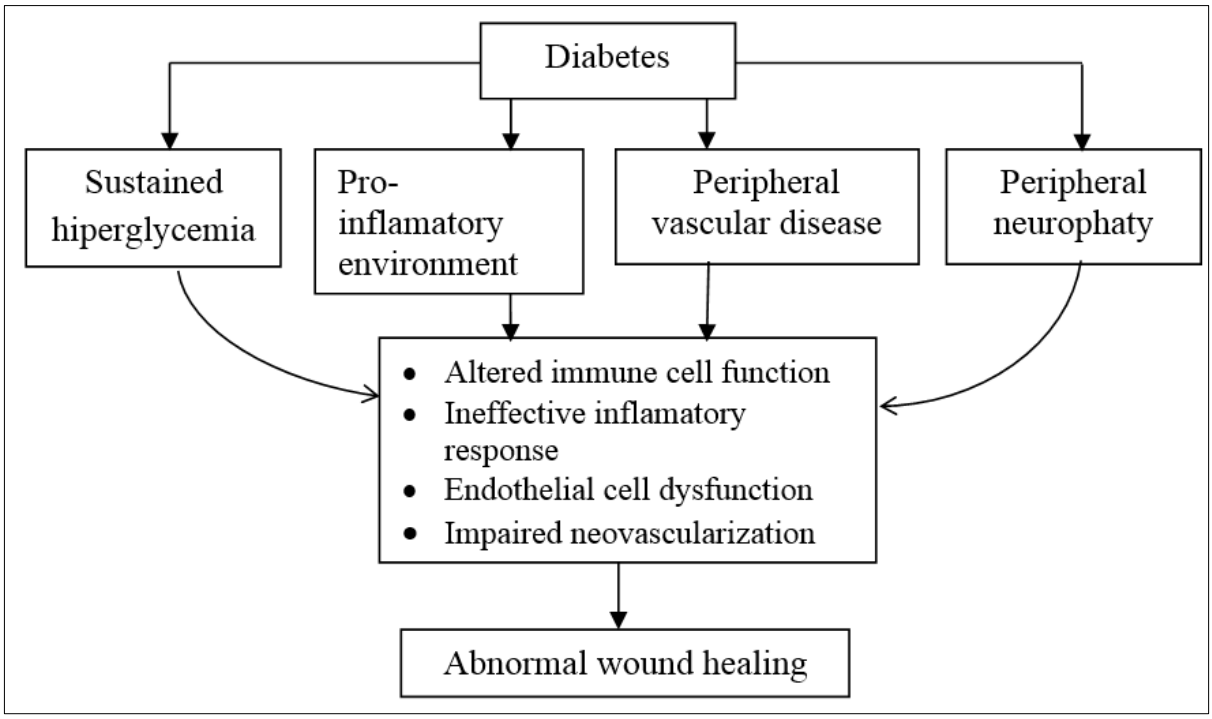

Figure 1: Wound healing disorders in diabetes.[7]

Haemostasis occurs within an hour after injury and is characterized by vasoconstriction and clotting. Platelets not only initiate the clotting cascade but also secrete growth factors and cytokines which initiate healing. Haemostasis occurs within an hour after injury and is characterized by vasoconstriction and clotting. Platelets not only initiate the clotting cascade but also secrete growth factors and cytokines which initiate healing. The subsequent inflammation phase takes up to seven days and is mediated through neutrophil granulocytes which prevent bacterial contamination and cleanse the wound from cell debris. The proliferation phase is initiated at day 2 after injury and takes up to 20 days. This phase is primarily characterized by tissue granulation and formation of new blood vessels (angiogenesis). The angiogenic process involves growth factors such as platelet-derived growth factor (PDGF), macrophage angiogenesis factor, and angiotensin. Concomitant epithelialisation is then initiated to cover the granulation tissue with a cellular barrier. The last phase involving extensive tissue remodelling lasts from one week to six months after injury. During that phase the provisional wound matrix is replaced with proteoglycan and collagen molecules which readily become organised into thicker bundles resulting in stronger but more rigid scar tissue.[4]

It has been postulated that hyperglycaemia itself has a deleterious effect on wound healing through the formation of advanced glycation end-products (AGEs) which induce the production of inflammatory molecules (TNF-α, IL-1) and interfere with collagen synthesis.[16] Furthermore, Spravchikov et al showed that exposure to high glucose was associated with changes in cellular morphology, decreased proliferation and abnormal differentiation of keratinocytes, thus revealing another mechanism by which hyperglycaemia may affect wound healing in diabetes.[17]

In DM, there is a decreasing in peripheral soft tissue healing ability that leads to ulcers. In diabetes, especially in the advanced stage where the structure of skin tissue, nerves, blood vessels and other support tissues have been damaged, so the control of blood glucose is no longer enough to fix them. Slow wound healing in DM will increase the risk of wound complications that will further slow wound healing. These complications include

infections (including cellulitis, abscesses and osteomyelitis), gangrene and septicemia.[18,19]

DISCUSSION

Types of diabetic foot ulcers[20]

According to Edmon diabetic foot ulcers are divided into 2 groups.

Neuropathic ulcers: Feet is warm, perfusion is still good with pulsation still palpable, perspiration is reduced, skin dry and cracked.

Neuroischemic ulcers: Feet is colder, not palpable pulsation, thin skin, smooth and without hair, subcutaneous tissue atrophy, intermittent claudication and rest pain may not be present due to neuropathy.

Classification of diabetic foot ulcer

There are several classifications of diabetic foot ulcers known today such as Wagner classification, University of Texas wound classification system (UT) and PEDIS. Criteria for diagnosis of infection in diabetic foot ulcers if there are 2 or more of the following signs: Swelling, induration, erythema around the lesion, local pain, palpable local warmth and presence of pus.[7,21] Infection is divided into mild infections (superficial, inner and limited in size), moderate (deeper and wider), severe (accompanied by systemic signs or metabolic disorders).[21]

Physical examination of diabetic foot ulcer[9]

Examination of ulcers and general circumstances of the extremities

Diabetic ulcers have a tendency to occur in some of the areas that become the largest loads of heels such as the heel, the area of the metatarsal head on the palm, the prominent fingertips. Other abnormalities found in the physical examiner include: hypertrophic callus, brittle or broken nail, hammer toes and fissure.

Assessment of possible vascular insufficiency

Physical examination shows the disappearance or decrease of the peripheral pulse below a certain level. bruits on the iliac and femoral arteries, skin atrophy, hair loss in the legs, cyanosis of the toes, ulceration and ischemic necrosis, both pale feet when the foot is raised as high as the heart for 1-2 minute.

Assessment of possible peripheral neuropathy

Peripheral neuropathy signs include loss of sensation of vibration and position, loss of deep tendon reflex, tropical ulceration, foot drop, muscle atrophy and hypertrophic callus formation especially in the pressure areas, on the heel.

Table 1: Wagner classification.[9]

Grade	Lesion
1.	Superficial diabetic ulcer
2.	Ulcer extension involving ligament, tendon, joint capsule, or fascia with no abscess or osteomyelitis
3.	Deep ulcer with abscess or osteomyelitis
4.	Gangrene to portion of forefoot
5.	Extensive gangrene of foot

Laboratory examination[9]

Blood tests

Leukocytosis may indicate an abscess or other infection of the foot.

Metabolic profile

Measurement of blood glucose, glychemhemlobin and serum creatinine helps to determine the adequacy of glucose regulation and renal function.

Radiological examination

It includes computed tomographic (CT) scan and magnetic resonance imaging (MRI) may be used to help diagnose an abscess if the physical examination is unclear.

Management and treatment modalities for diabetic ulcers

The management of diabetic foot ulcers includes several facets of care. The main goal in the management of diabetic ulcers is the closure of the wound.[22] Treatment of DFU wound in DM patients is carried out constantly with the type of action depending on the severity of the ulcer and the presence or absence of ischemia. The basis of DFU therapy is necrotomy/ debridement, reducing the load/pressure on the area of the injury (offloading), manage the infection by diagnosing the type of bacteria, providing adequate antibiotics and ulcer treatment using wound dressing clean and moist.[23,24]

Debridement is an act of disposing of non-living materials, foreign bodies and unhealthy tissues that are difficult to recover from injury.[25] Debridement should be performed on all chronic wounds to remove necrotic tissue and debris.[26,27] The debridement of the wound will include the removal of surrounding callus and will aid in decreasing pressure points at callused sites on the foot. Additionally, the removal of unhealthy tissue can aid in removing colonizing bacteria in the wound. It will also facilitate the collection of appropriate specimens for

culture and permit examination for the involvement of deep tissues in the ulceration.[4]

Offloading is a reduction in pressure on the ulcer, becoming one of the components of diabetes ulcer management. Ulceration usually occurs in the area of the foot that gets high pressure. Bed rest is an ideal way to reduce pressure but it is difficult to do total contact casting (TCC) is the most effective offloading method. TCC is made of specially formed casts to spread the patient's burden out of the ulcer area.[7]

Management of infection

Because of the high incidence rate of infection in diabetic ulcers, a systemic approach is required for a complete assessment. The diagnosis of infection is primarily based on clinical conditions such as erythema, edema, pain, softness, warmth and discharge from pus.[28] If infection is suspected in the wound, the selection of appropriate treatments should be based on the results of a wound culture. Tissue curettage from the base of the ulcer after debridement will reveal more accurate results than a superficial wound swab. In the case of deep tissue infections, specimens obtained aseptically during surgery provide optimal results.[29]

Mild and moderate infections may be treated for polyclinics by oral antibiotics, such as cephalexin, amoxilin-clavulanic, moxifloxin or clindamycin.[30,31] The choice of intravenous antibiotics for severe infections includes imipenem-cilastatin, β-lactam β-lactamase (ampicillin-sulbactam and piperacilintazobactam) and broad-spectrum cephalosporin.[30]

The selection of appropriate antimicrobial therapy, including the agent, route of administration and need for inpatient or outpatient treatment will be determined in part by the severity of the infection. Besides all these conventional methods to manage diabetic ulcers, acceleration of wound healing by using some surgical dressings or topical application of some growth factors may become an option.

The main purpose of a closed dressing is to provide a humid healing environment to facilitate cell migration and prevent dry sores. The choice of dressing depends on the number and type of exudates present in the wound. Hydrogel dressing, film, composite is well used for cuts with a small amount of exudates. For wounds with exudates amounts being used hydrocolloids and for wounds with exudates amount widely used alginate and foam.[7] Topical or local application of mixture of some growth factors like platelet rich plasma (PRP) and extract of amniotic or placental fluids can also accelerate rate of wound healing. Additional current treatment methods in persistent diabetic foot ulcers are autologous skin transplantation, tissue-engineered human skin, another very promising therapeutic option involves the use of bone marrow-derived cells, and recent evidence indicates that bone marrow contains stem cells with the potential for differentiation into a variety of tissues. Other than these sub-atmospheric pressure dressings like vacuum-assisted closure device have been shown to be an effective way in accelerating the healing of various wounds.[3]

CONCLUSION

Diabetic foot management is inclusion of treatment of diabetic control, improvement of blood circulation, control of infection along with debridement and dressing. There are many researches going on for newer modalities for dressing for fastening wound healing. But long term benefit and costing ratio is still awaited. More recently, PRP and placenta extract helps in healing of diabetic ulcer. Still comparative study between both the newer modalities are not much documented in literature.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(2):217-28.
2. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. Wound Repair Regenerat. 2005;13(3):230-6.
3. Hunt TK. Basic principles of wound healing. J Trauma Acute Care Surg. 1990;30:122-8.
4. Tsourdi E, Barthel A, Rietzsch H, Reichel A, Bornstein SR. Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus. BioMed Res Int. 2013;2013.
5. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol. 2014;70(1):1-18.
6. Wang A, Xu Z, Ji L. Clinical characteristics and medical costs of diabetics with amputation at central urban hospitals in China. Zhonghua Yi Xue Za Zhi. 2012;92(4):224-7.
7. Rosyid FN. Etiology, pathophysiology, diagnosis and management of diabetics' foot ulcer. Int J Res Med Sci. 2017;5(10):4206-13.
8. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med. 1998;158(2):157-62.
9. Clayton W, Elasy TA. A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. Clin Diabetes. 2009;27(2):52-8.
10. Bowering CK. Diabetic foot ulcers. Pathophysiology, assessment, and therapy. Canadian Fam Phys. 2001;47:1007.

11. Dyck PJ, Davies J, Wilson D. Risk factors for severity of diabetic polyneuropathy. Diabetes Care. 1999;22(9):1479-86.
12. Huijberts MS, Schaper NC, Schalkwijk CG. Advanced glycation end products and diabetic foot disease. Diabetes Metabol Res Rev. 2008;24(1):19-24.
13. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care. 2008;31(8):1679-85.
14. Zochodne DW. Diabetic polyneuropathy: an update. Curr Opin Neurol. 2008;21(5):527-33.
15. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiologic Rev. 2003;83(3):835-70.
16. Hennessey PJ, Ford EG, Black CT, Andrassy RJ. Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats. J Pediatr Surg. 1990;25(1):75-8.
17. Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. Glucose effects on skin keratinocytes: implications for diabetes skin complications. Diabetes. 2001;50(7):1627-35.
18. Wild T, Rahbarnia A, Kellner M, Sobotka L, Eberlein T. Basics in nutrition and wound healing. Nutrition. 2010;26(9):862-6.
19. Sharp A, Clark J. Diabetes and its effects on wound healing. Nurs Standard. 2011;25(45).
20. Edmonds M. Diabetic foot ulcers. Type Diabetes. 2016:327-40.
21. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 infectious diseases society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):132-73.
22. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, et al. Diabetic foot ulcers: part II. Management. J Am Acad Dermatol. 2014;70(1):21-4.
23. Rebolledo FA, Soto JT, Peña JE. The pathogenesis of the diabetic foot ulcer: prevention and management. Glob Perspect Diabet Foot Ulcerat. 2011:155-78.
24. McIntosh C, Kelly L. Importance of wound debridement in management of diabetic foot ulcers: Case report. Wound Essent. 2009;4:122-5.
25. Shankhdhar K, Shankhdhar L, Shankhdhar U, Shankhdhar S. A case report: offloading the diabetic foot wound in the developing world. J Diab Foot Comp. 2011;3(2):26-9.
26. Wu SC, Driver VR, Wrobel JS, Armstrong DG. Foot ulcers in the diabetic patient, prevention and treatment. Vascul Health Risk Manage. 2007;3(1):65.
27. Lebrun E, Tomic-Canic M, Kirsner RS. The role of surgical debridement in healing of diabetic foot ulcers. Wound Repair Regenerat. 2010;18(5):433-8.
28. Webster J, Scuffham P, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. Coch Database Systemat Rev. 2014(10).
29. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004:885-910.
30. Jones R. Exploring the complex care of the diabetic foot ulcer. JAAPA. 2007;20(2):3.
31. Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Phys. 2002;66(9):1655.

Cite this article as: Panchakshari MK, Patel NJ, Thakkar NB, Patel KK. Pathogenesis, diagnosis and management of diabetic foot ulcers: a systematic review. Int J Res Med Sci 2022;10:2717-21.