Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2018; SP6: 48-55

Dr. MV Kumudhavalli
Professor, Department of Pharmaceutical Chemistry, Vinayaka Missions College of Pharmacy, Vinayaka Missions University, Salem, Tamilnadu, India

Pawar Kirteebala
Assistant Professor, Department of Pharmaceutics, Ideal College of Pharmacy and Research, Kalyan, Maharashtra, India

Pawar Archana
Final Year B. Pharm, Konkan Gyanpeeth College of Pharmacy and Research Institute, Karjat, Maharashtra, India

Correspondence
Dr. MV Kumudhavalli
Professor, Department of Pharmaceutical Chemistry, Vinayaka Missions College of Pharmacy, Vinayaka Missions University, Salem, Tamilnadu, India

(Special Issue- 6)
Innovation development and standardization of Novel Herbal Formulation
(September 24-25, 2018)

Diabetic foot ulcer: A review

Dr. MV Kumudhavalli, Pawar Kirteebala and Pawar Archana

DOI: https://doi.org/10.22271/phyto.2018.v7.isp6.1.12

Abstract
The disease of diabetes is one of the important problems of the world and the number of patients suffering from it, is growing day by day. Diabetic foot ulcer is a devastating component of diabetes progression and is caused by loss of glycemic control, peripheral neuropathy, peripheral vascular disease and immunosuppression. An estimated 15% of patients with diabetes have diabetic foot ulcers, during their lifetime. The aim of the present review is to summarize the cause, pathogenetic mechanisms leading to diabetic foot and to focus on the treatment and the management of this important health issue.

Keywords: DFU, Diabetes mellitus, Lesions, Diabetic foot ulcers

Introduction
Diabetes mellitus (DM) is one of the main problems in health systems and a global public health threat that has increased dramatically over the past 2 decades [1 ,2].Patients with DM are prone to multiple complications such as diabetic foot ulcer (DFU). DFU is a common complication of DM that has shown an increasing trend over previous decades [3-5]. Diabetic foot ulcers are one of several serious complications of diabetes progression. Major contributing causes to diabetic foot ulcers are peripheral neuropathy, peripheral arterial disease, and immunosuppression [6-8]. Up to 15% of patients with diabetes have diabetic foot ulcers, and these ulcers lead to more than 80,000 amputations per year in the United States [9, 10]. The lifetime risk of diabetic foot ulcers for patients with diabetes may reach up to 68 per 1,000 persons as reported by some studies [11]. The majority (60–80%) of foot ulcers will heal, while 10-15% of them will remain active, and 5-24% of them will finally lead to limb amputation within a period of 6-18 months after the first evaluation. Neuropathic wounds are more likely to heal over a period of 20 weeks, while neuroischemic ulcers take longer and willmore often lead to limb amputation [12]. It has been found that 40-70% of all no traumatic amputations of the lower limbs occur in patients with diabetes [13].
The risk of foot ulceration and limb amputation increases with age and the duration of diabetes [14, 15].

Pathogenesis
Recent studies have indicated multiple risk factors associated with the development of DFU [16-19]. These risk factors are as follows: gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index, and other comorbidities such as retinopathy, diabetic peripheral neuropathy, peripheral arterial disease, glycated hemoglobin level (HbA1C), foot deformity, high plantar pressure, infections, and inappropriate foot self-care habits [18-22]. (Figure 1).Peripheral arterial disease is 2-8 times more common in patients with diabetes, starting at an earlier age, progressing more rapidly, and usually being more severe than in the general population. It commonly affects the segments between the knee and the ankle. It has been proven to be an independent risk factor for cardiovascular disease as well as a predictor of the outcome of foot ulceration [23]. In patients with peripheral diabetic neuropathy, loss of sensation in the feet leads to repetitive minor injuries from internal (calluses, nails, foot deformities) or external causes (shoes, burns, foreign bodies) that are undetected at the time and may consequently lead to foot ulceration. This may be followed by

infection of the ulcer, which may ultimately lead to foot amputation, especially in patients with peripheral arterial disease. Structural foot deformities and abnormalities, such as flatfoot, hallux valgus, claw toes, Charcot neuroarthropathy, and hammer foot, play an important role in the pathway of diabetic foot ulcers since they contribute to abnormal plantar pressures and therefore predispose to ulceration. Other risk factors for foot ulceration include a previous history of foot ulceration or amputation, visual impairment, diabetic nephropathy, poor glycemic control, and cigarette smoking. Some studies have shown that foot ulceration is more common in men with diabetes than in women [24, 25]. Immune changes include reduced healing response in diabetic foot ulcers. Increased T lymphocyte apoptosis, which inhibits healing, has been observed in patients with diabetic foot ulcers [26].

In total, the most common pathway to develop foot problems in patients with diabetes is peripheral sensorimotor and autonomic neuropathy that leads to high foot pressure, foot deformities, and gait instability, which increases the risks of developing ulcers [27-29].

Assessment and Diagnosis

Patients with diabetes should be assessed for arterial insufficiency and neuropathic disease on a structured schedule based on defined risk factors. Assess the patient's temperature, respirations, heart rate, and BP in both extremities and document any abnormalities [30]. People with diabetes are at high risk of developing peripheral vascular disease; therefore, the palpation of pulses bilaterally in the dorsalis pedis, posterior tibial, popliteal, and superficial femoral arteries is necessary for assessment of the blood circulation in the lower limbs. Inadequate perfusion of a limb, due to peripheral vascular disease, may crucially affect the progress of the healing of an ulcer, often resulting in chronic unhealed ulcers that are susceptible to infection [31]. A relatively simple method to confirm the clinical suspicion of arterial occlusive disease is to measure the resting systolic blood pressure in the ankles and arms. This is performed by measuring the systolic blood pressure (using a Doppler probe) in the brachial, posterior tibial, and dorsalis pedis arteries [32]. The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements. This ratio is referred to as the ankle–brachial index (ABI). Normal ABI values range from 1.0 to 1.3, since the pressure is higher in the ankle than in the arm. Values over 1.3 suggest a noncompressible calcified vessel. An ABI of less than 0.9 is indicative of peripheral vascular disease and is associated with 50% or more stenosis in one or more major vessels. An ABI of 0.4–0.9 suggests a degree of arterial obstruction associated with claudication. An ABI of less than 0.4 or an ankle systolic pressure of less than 50 mmHg represents advanced ischemia [33].

Symptoms of neuropathic disease include numbness, paresthesia, and burning sensations. All patients with diabetes should be assessed regularly for loss of protective sensation; any of the following five tests may be used.

• The 10-g monofilament test determines a patient's sensitivity to touch. With the patient's eyes closed, touch the monofilament to one or more anatomic sites, including reference sites to verify sensation detection; inability to detect this touch at the test site indicates loss of large nerve fiber function. Test the first, third, and fifth metatarsal heads and the plantar surface of the distal hallux.

• A 128-Hz tuning fork used to detect vibratory sensation. This test uses a tuning fork held bilaterally over the toes to elicit vibratory sensation. Have the patient close his or her eyes. To conduct the test, touch the base of a vibrating 128-Hz tuning fork to a bony surface of each bare toe in succession, and ask the patient to acknowledge when the vibration is felt and when it is removed.

• A pinprick test is administered just proximal to the toenail of the dorsal aspect of the hallux. Inability to detect the pinprick is an abnormal result and indicates neuropathy.

• The ankle reflexes test of the Achilles tendon is done with the patient sitting in a chair or on an examination table. Place the foot in a neutral position, slightly stretching the Achilles tendon. Strike the tendon with a tendon hammer. If no tendon response occurs, ask the patient to lock his or her fingers together and pull; then retest the tendon reflex. Absence of an ankle reflex is an abnormal result that may indicate peripheral neuropathy.

• The vibration perception threshold test uses a biothesiometer to make a semiquantitative assessment of the patient's vibration perception threshold (VPT). With the patient lying supine, a VPT is measured at a proximal control site by placing the instrument stylet on the skin and increasing the amplitude until vibration is detected. VPT measurement is then conducted at each hallux using the mean of three measurements for each. A VPT greater than 25 V has been correlated with later development of diabetic foot ulcers [34].

Classification of Foot Lesions in Diabetes Mellitus

For evaluation and determination of the severity of diabetic foot, various classification systems are in use now, that attempt to encompass different characteristics of an ulcer (namely site, depth, the presence of neuropathy, infection, and ischemia, etc.) [35-41] including Wagner System, University of Texas System and a hybrid System, Depth Ischemic classification, the PEDIS System. It seems that poor clinical outcomes are generally associated with infection, peripheral vascular disease, and increasing wound depth; it also appears that the progressive cumulative effect of these comorbidities contribute to a greater likelihood of a diabetic foot ulcer leading to a lower-limb amputation.

The three main diabetic foot classification system are discussed that are commonly used in clinical diagnosis of diabetic foot.

These were:

1. Wagner-Meggitt Classification
2. Depth-Ischemic classification 3.3. University of Texas classification
3. Meggit-Wagner Classification

Most common and widely used Classification system is the Wagner Diabetic Foot classification System (Table 1). This system is basically anatomical with gradations of superficial ulcer, deep ulcer, abscess osteitis, gangrene of the fore foot, and gangrene of the entire foot. Only grade 3 addresses the problem of infection. In this system foot lesions are divided into different grades starting from grade 0 to grade 5. Grade 0 includes high risk foot but no active lesion and grade 5 includes gangrene of entire foot. But this system does not mention about ischemia or neuropathy and that is the drawback of this system.

Depth-Ischemic Classification

This classification is a modification of Wagner-Meggit system. The purpose of this classification system is to make the classification more accurate, rational, easier to distinguish between wound and vascularity of foot, to elucidate the

difference among the grades 2 and 3, and to improve the correlation of treatment to the grade. Details of depth Ischemic classification are presented in table 2.

University of Texas Classification System

Another popular system is the University of Texas San Antonio System which incorporates lesion depth and ischemia (Table 3). It is actually a modification of Wagner System .In this system each grade of Wagner System is further divided into stages according to the presence of infection or ischemia or combination of both. This system is somewhat superior in predicting the outcome in comparison to the Wagner System [42, 43].

Table 1: Wagner-Meggitt Classification System.

Grade	Lesion
0	No open Lesion
1	Superficial ulcer
2	Deep ulcer to tendon or joint capsule
3	Deep ulcer with abscess, osteomyelitis
4	Local gangrene- fore foot or heel
5	Gangrene of entire foot

Table 2: Depth Ischemic classification System.

Grade	Lesion
0	No open lesions: may have deformity or cellulitis
A Ischemic	B Infected
1	Superficial ulcer
A Ischemic	B Infected
2	Deep ulcers to tendon, or joint capsule
A Ischemic	B Infected
3	Deep ulcers with abscess, osteomyelitis, or joint sepsis
A Ischemic	B Infected
4	Localized gangrene — forefoot or heel
A Ischemic	B Infected
5	Gangrene of entire foot
A Ischemic	B Infected

Table 3: University of Texas Classification System

Stages	Grade			
	0	I.	II.	III.
A	Pre-or post-ulcerative lesions Completely epithelialized	Superficial wound not involving tendon capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

Treatment

The gold standard for diabetic foot ulcer treatment includes debridement of the wound, management of any infection, revascularization procedures when indicated, and off-loading of the ulcer [28]. Other methods have also been suggested to be beneficial as add-on therapies, such as hyperbaric oxygen therapy, use of advanced wound care products, and negative pressure wound therapy (NPWT) [44].

Debridement

Ulcer debridement removes necrotic tissue, foreign material such as bacteria, and hyperkeratosis that may surround the wound [45]. Sharp debridement using a scalpel cleans the wounds, excises the margins, and exposes a healthy tissue granulation base for epithelial layer regeneration; specimens also may be taken at this time for culture [46-48]. Selective sharp debridement followed by saline-moistened gauze has been used widely in managing diabetic foot ulcers [49]. Superficial ulcer debridement can usually be carried out in the clinic or at the bedside using local anesthesia, where necessary. Local anesthesia may not be required with more advanced manifestations of peripheral neuropathy. Advanced ulcers requiring deep tissue debridement require surgery in the OR so that appropriate specimens for culture can be obtained [45]. Chemical debridement is an alternative to sharp or mechanical debridement. Clostridial collagenase ointment debridement has been shown to provide improved healing of diabetic foot ulcers [49]. A study by Tallis and colleagues found that clostridial collagenase ointment debridement reduced mean wound area significantly compared with selective sharp debridement followed by saline-moistened gauze [49]. In addition, economic analysis indicated that clostridial collagenase ointment is cost-effective in multiple care settings. Other debridement methods include hydrocolloid and hydrogel dressings, which facilitate autolysis of necrotic wound tissue but cannot be used on infected wounds. Alginate and silver-impregnated dressings and maggot debridement therapy also may be appropriate [50]. However, there is no substitute for adequate wound debridement, appropriate systemic antibiotic therapy, and daily dressing changes and wound inspection [51].

Autolytic debridement involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body's enzymes. Autolysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels, and films. Autolysis is highly selective, avoiding damage to the surrounding skin [52].

In conclusion, debridement, especially the ''sharp method,'' is one of the gold standards in wound healing management, significantly contributing to the healing process of the wound, including the diabetic ulcer [53, 54].

Offloading

The use of offloading techniques, commonly known as pressure modulation, is considered the most important component for the management of neuropathic ulcers in patients with diabetes [55, 56]. Recent studies have provided evidence indicating that proper offloading promotes DFU healing [57-59]. Although many offloading modalities are

currently in use (Table 2), only a few studies describe the frequency and rate of wound healing with some of the methods frequently used clinically. The choice of these methods is determined by patient physical characteristics and abilities to comply with the treatment along with the location and severity of the ulcer [56]. The most effective offloading technique for the treatment of neuropathic DFU is total contact casts (TCC) [56, 60, 61]. TCC is minimally padded and molded carefully to the shape of the foot with a heel for walking (Figure 1). The cast is designed to relieve pressure from the ulcer and distribute pressure over the entire surface of the foot; thus, protecting the site of the wound [56]. Mueller *et al* [61] conducted an RCT that showed TCC healed a higher percentage of plantar ulcers at a faster rate when compared with the standard treatment. In addition, a histologic examination of ulcer specimens has shown that patients treated with TCC before debridement had better healing as indicated by angiogenesis with the formation of granulation tissue than for patients treated with debridement alone as indicated by a predominance of inflammatory elements [62]. The contributory factors to the efficacy of TCC treatment are likely to be due to pressure redistribution and offloading from the ulcer area. In addition, the patient is unable to remove the cast, which thereby forces compliance, reduces activity levels, and consequently improves wound healing [58]. However, the frequency of side effects referred to in the literature and minimal patient acceptance make this approach inappropriate for wide applications [63, 64]. Fife *et al* [65] has shown that TCC is vastly underutilized for DFU wound care in the United States. Based on this study, only 16% of patients with DFU used TCC as their offloading modalities. The main disadvantage of TCC was the need for expertise in its application. Most centers do not have a physician or cast technician available with adequate training or experience to safely apply TCC. In addition, improper cast application can cause skin irritation and in some cases even frank ulceration. Also, the expense of time and materials (the device should be replaced weekly), limitations on daily activities (e.g., bathing), and the potential of a rigid cast to injure the insensate neuropathic foot are considered other disadvantages. Furthermore, TCC does not allow daily assessment of the foot or wound, which is often contraindicative in cases of soft tissue or bone infections [57, 66, 67]. In some cases, it is suggested to use other kinds of offloading techniques such as a removable cast walker (RCW) or Instant TCC (iTCC). An RCW is cast-like device that is easily removable to allow for self-inspection of the wound and application of topical therapies that require frequent administration [56, 64] (Figure 2). The application of this method allows for bathing and comfortable sleep. In addition, because RCW is removable, they can be used for infected wounds as well as for superficial ulcers [56]. However, in a study that compared the effectiveness of TCC, RCW, and half-shoe, this method did not show equivalent healing time (mean healing time: 33.5, 50.4, and 61.1 d, respectively), and asignificantly higher proportion of people with DFU were healed after 12 wk wearing a TCC compared with the two other widely used offloading modalities [81]. iTCC, which involves simply wrapping a RCW with a single layer of cohesive bandage, Elastoplast or casting tape is another offloading technique that is shown to be more effective than TCC [68] and RCW [69]. This technique forces the patient to adhere to advice to immobilize the foot while allowing for ease of application and examination of the ulcer as needed. A preliminary randomized trial of TCC vs iTCC in the management of plantar neuropathic foot ulcers has confirmed equivalent efficacy of the two devices and that iTCC is cheaper, quicker to apply, and has fewer adverse effects than traditional TCC [69]. As this device does not require a skilled technician to apply it, it could revolutionize the future management of plantar neuropathic ulcers. It has been suggested that iTCC will dramatically change the treatment of non-ischemic, neuropathic, diabetic plantar ulcers, and has the potential to replace TCC as the gold standard for offloading plantar neuropathic ulcers [68]. Regardless of the modality selected, patients should return to an unmodified shoe until complete healing of the ulcer has occurred (Figure 3). Furthermore, any shoe that resulted in the formation of an ulcer should not be worn again [70].

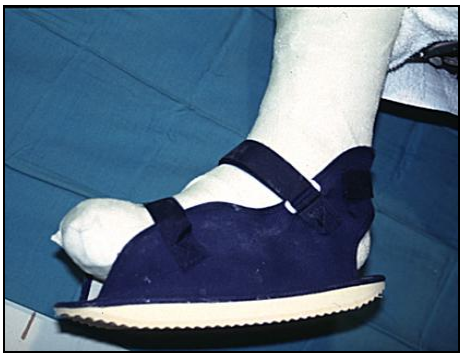

Fig 1: Total contact cast for patients with diabetic foot ulcer. (Data adopted from Armstrong *et al* [56]

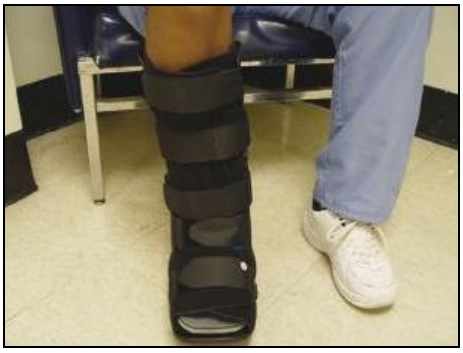

Fig 2: Removable cast walker (DH Walker) for patients with diabetic foot ulcer. (Data adopted from Rathur *et al*)[60]

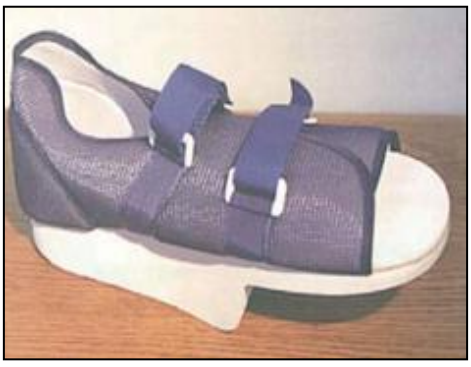

Fig 3: Half shoe for off-loading pressure from the foot of a diabetic patient with foot ulcer. (Data adopted from Armstrong *et al*) [56]

Dressings

Ulcers heal more quickly and are often less complicated by infection when in a moist environment. The only exception isdry gangrene, where the necrotic area should be kept dry in order to avoid infection and conversion to wet gangrene. A wound's exudate is rich in cytokines, platelets, white blood

cells, growth factors, matrix metalloproteinases (MMPs), and other enzymes. Most of these factors promote healing via fibroblast and keratinocyte proliferation and angiogenesis, while others, such as leukocytes and toxins produced by bacteria, inhibit the healing process. Moreover, it has been reported that local concentrations of growth factors [platelet-derived growth factorbeta (PDGF-beta), transforming growth factorbeta] are low in patients with chronic ulcers [71]. The ideal dressing should be free from contaminants, be able to remove excess exudates and toxic components, maintain a moist environment at the wound-dressing interface, be impermeable to microorganisms, allow gaseous exchange, and, finally, should be easily removed and cost-effective [72]. Various dressings are available that are intended to prevent infection and enhance wound healing, and several studies support their effectiveness for this purpose [73, 74]. However, most of these studies were performed in wounds and not in diabetic ulcers [71, 73, 74]. Available data on their use in diabetes are scarce [54], and therefore further randomized clinical trials are needed to support the existing evidence for their benefit in diabetic ulcers.

Electrical stimulation

Electrical stimulation (ES) has been reported as a perfect adjunctive therapy for DFU healing in recent literature. Currently, there is a substantial body of work that supports the effectiveness of ES for DFU healing [75-78]. In a randomized, double-blind, placebo-controlled trial study conducted by Peters *et al* [75] on 40 patients with DFU, significant differences in number of healed ulcers (65% in treatment group vs 35% in control group) were found at 12 wk. Based on the literature review, it is suggested that ES could improve common deficiencies that have been associated with faulty wound healing in DFU, such as poor blood flow, infection, and deficient cellular responses [75, 79]. This therapy is a safe, inexpensive, and a simple intervention to improve wound healings in patients with DFU [79, 80].

Growth factors

DFU has demonstrated the benefits from growth factors (GFs) such as platelet derived growth factor (PDGF), fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factors (IGF1, IGF2), epidermal growth factor, and transforming growth factor b [81]. Among the aforementioned GFs, only recombinant human PDGF(rhPDGF) (Becaplermin or Regranex), which is a hydrogel that contains 0.01% of PDGF-BB (rhPDGF-BB), has demonstrated increased healing rates when compared with controls in a number of clinical trials [82-85] and has shown sufficient DFU repair efficacy to earn Food and Drug Administration (FDA) approval[86]. In one randomized placebo controlled trial involving patients with full thickness DFU, Becaplermin demonstrated a 43% increase in complete closure vs placebo gel (50% vs 35%) [87]. In another randomized placebo-controlled trial, Sibbald *et al.* [88] demonstrated that patients with infection-free chronic foot ulcers treated with the best clinical care and oncedaily applications of 100 μg/g Becaplermin gel had a significantly greater chance of 100% ulcer closure by 20 wk than those receiving the best clinical care plus placebo (vehicle gel) alone. GFs have been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes, and other components that form the cellular basis of wound healing [82, 89].

References

1. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). Pak J Med Sci. 2013; 29:730-734 [PMID: 24353617 DOI: 10.12669/pjms.293.3473]
2. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. World J Diabetes. 2012; 3:110-117. [PMID: 22737281 DOI: 10.4239/wjd. v3.i6.110]
3. Aalaa M, Malazy OT, Sanjari M, Peimani M, Mohajeri Tehrani M. Nurses' role in diabetic foot prevention and care; a review. J Diabetes Metab Disord. 2012; 11:24 [PMID: 23497582 DOI: 10.1186/2251-6581-11-24]
4. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, Woo K *et al*. Diabetic foot ulcers: Part II. Management. J Am Acad. Dermatol. 2014; 70:21.e1-2124; quiz 21.e1-2124 [PMID: 24355276 DOI: 10.1016/j.jaad.2013.07.048]
5. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005; 366:1725-1735 [PMID: 16291067 DOI: 10.1016/S0140-6736(05)67699-4]
6. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classifi cation. Am Fam Physician. 1998; 57(6):1352-1332, 1337-1338.
7. Bowering CK. Diabetic foot ulcers. Pathophysiology, assessment, and therapy. Can Fam Physician. 2001; 47:1007-1016.
8. Dinh T, Tecilazich F, Kafanas A, *et al*. Mechanisms involved in the development and healing of diabetic foot ulceration. Diabetes. 2012; 61(11):2937-2947.
9. Reiber GE. The epidemiology of diabetic foot problems. Diabet Med. 1996; 13(1):6-11.
10. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005; 366(9498):1719-1724.
11. Lavery LA, Armstrong DG, Wunderlich RP *et al*. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-hispanic whites from a diabetes disease management cohort. Diabetes Care. 2003; 26(5):1435-1438.
12. Katsilambros N, Dounis E, Makrilakis K, Tentolouris N, Tsapogas P. Atlas of the diabetic foot. 2nd ed. Oxford: Wiley-Blackwell, 2010.
13. Moxey PW, Gogalniceanu P, Hinchliffe RJ, *et al*. Lower extremity amputations-a review of global variability in incidence. Diabet Med 2011; 28:1144-53.
14. 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; 158:157-62.
15. Malgrange D, Richard JL, Leymarie F. French working group on the diabetic foot. Screening diabetic patients at risk for foot ulceration. A multicentre hospital-based study in France. Diabetes Metab. 2003; 29:261-8.
16. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR *et al*. Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg. 2006; 45:1-66 [PMID: 17280936 DOI: 10.1016/ S1067-2516(07)60001-5]
17. Bortoletto MS, De Andrade SM, Matsuo T, Haddad Mdo C, González AD, Silva AM. Risk factors for foot ulcers--a cross sectional survey from a primary care setting in

Brazil. Prim Care Diabetes. 2014; 8:71-76. [PMID: 23639609 DOI: 10.1016/ j.pcd.2013.04.003]
18. Waaijman R, De Haart M, Arts ML, Wever D, Verlouw AJ, Nollet F *et al*. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care. 2014; 37:1697-1705 [PMID: 24705610 DOI: 10.23 37/dc13-2470]
19. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis Ribeiro M. Predictive factors for diabetic foot ulceration: asystematic review. Diabetes Metab Res Rev. 2012; 28:574-600 [PMID: 22730196 DOI: 10.1002/dmrr .2319]
20. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). Pak J Med Sci 2013; 29:730-734. [PMID: 24353617 DOI: 10.12669/ pjms.293.3473]
21. Iraj B, Khorvash F, Ebneshahidi A, Askari G. Prevention of diabetic foot ulcer. Int J Prev Med. 2013; 4:373-376. [PMID: 23626896]
22. McEwen LN, Ylitalo KR, Herman WH, Wrobel JS. Prevalence and risk factors for diabetes-related foot complications in Translating Research into Action for Diabetes (TRIAD). J Diabetes Complications. 2013; 27:588-592. [PMID: 24035357 DOI: 10.1016/j.jdiacomp.2013.08.003]
23. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Eur J Vasc Endovasc Surg. 2000; 19(A):1-250.
24. Prompers L, Huijberts M, Apelqvist J *et al*. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007; 50:18-25.
25. Benotmane A, Mohammedi F, Ayad F, Kadi K, Azzouz A. Diabetic foot lesions: etiologic and prognostic factors. Diabetes Metab. 2000; 26:113-7.
26. Arya AK, Garg S, Kumar S *et al*. Estimation of lymphocyte apoptosis in patients with chronic non-healing diabetic foot ulcer. Int J Med Sci Pub Health. 2013; 2(4):766-768.
27. Formosa C, Gatt A, Chockalingam N. Diabetic foot complications in Malta: prevalence of risk factors. Foot (Edinb) 2012; 22:294-297 [PMID: 22981100 DOI: 10.10 16/j.foot.2012.08.008]
28. Malgrange D. [Physiopathology of the diabetic foot]. Rev Med Interne. 2008; 29(2):231-237. [PMID: 18822248 DOI: 10.1016/S0248-8663(08)73950-X]
29. Sawacha Z, Gabriella G, Cristoferi G, Guiotto A, Avogaro A, Cobelli C. Diabetic gait and posture abnormalities: a biomechanical investigation through three dimensional gait analysis. ClinBiomech (Bristol, Avon). 2009; 24:722-728. [PMID: 19699564 DOI: 10.10 16/j.clinbiomech.2009.07.007]
30. Sumpio BE. Contemporary evaluation and management of the diabetic foot. Scientifi ca, 2012, 435-487
31. Boulton AJ. The diabetic foot-an update. Foot Ankle Surg. 2008; 14:120-4.
32. Hoffman AF. Evaluation of arterial blood flow in the lower extremity. Clin Podiatr Med Surg. 1992; 9:19-56.
33. Puttemans T, Nemery C. Diabetes: the use of color Doppler sonography for the assessment of vascular complications. Eur J Ultrasound. 1998; 7:15-22.
34. Boulton AJ, Armstrong DG, Albert SF *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):1679-1685.
35. Oakley W, Caterall CF. Aetiology and management of lesions of the feet in diabetes. Br Med J. 1956; 27:953-955.
36. Shea JD. Pressure sores: classification and management. ClinOrthop. 1975; 112:89-100.
37. Wagner FW. The dysvascular foot: a system of diagnosis and treatment. Foot Ankle. 1981; 2:64-122.
38. Knighton DR, Ciresi KF, Fiegel VD *et al*. Classification and treatment of chronic nonhealing wounds: successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986; 204:332-330.
39. Kaufman J, Breeding L, Rosenberg N. Anatomical location of acute diabetic foot infection: its influence on the outcome of treatment. Am Surg. 1987; 53:109-112.
40. Jones EW, Peacock I, McLain S *et al*. A clinicopathological study of diabetic foot ulcers. Diabet Med. 1987; 4:475-479.
41. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg. 1996; 35:528-531.
42. Apelqvist J, Castenfors J, Larsson J. Wound classification is more important than site of ulceration in the outcome of diabetic foot ulcers. Diabet Med. 1989; 6:526-530.
43. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. Am. J Surg. 1998; 176(2A):5-10.
44. Hinchliffe RJ, Valk GD, Apelqvist J *et al*. Specific guidelines on wound and wound-bed management. Diabetes Metab Res Rev. 2008; 24(1):188-9.
45. Lipsky BA, Berendt AR, Cornia PB *et al*. Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012; 54(12):132-173.
46. Sumpio BE. Contemporary evaluation and management of the diabetic foot. Scientifi ca, 2012, 435-487.
47. Boulton AJ, Armstrong DG, Albert SF *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):1679-1685.
48. Lipsky BA, Peters EJ, Senneville E *et al*. Expert opinion on the management of infections in the diabetic foot. Diabetes Metab Res Rev. 2012; 28(1):163-178.
49. Tallis A, Motley TA, Wunderlich RP *et al*. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. Clin Ther. 2013; 35(11):1805-1820.
50. Marineau ML, Herrington MT, Swenor KM, Eron LJ. Maggot debridement therapy in the treatment of complex diabetic wounds. Hawaii Med J. 2011; 70(6):121-124.
51. Hilton JR, Williams DT, Beuker B *et al*. Wound dressings in diabetic foot disease. Clin Infect Dis. 2004; 39(2):100-103.
52. Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis. 2004; 39(2):100-3.
53. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. Wound Repair Regen. 2002; 10:354-9.
54. Game FL, Hinchliffe RJ, Apelqvist J *et al*. A systematic review of interventions to enhance the healing of chronic

ulcers of the foot in diabetes. Diabetes Metab Res Rev. 2012; 28(1):119-41.
55. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001; 24:1019-1022. [PMID: 11375363 DOI: 10.2337/diacare. 24.6.1019]
56. Armstrong DG, Lavery LA, Nixon BP, Boulton AJ. It's not what you put on, but what you take off: techniques for debriding and off-loading the diabetic foot wound. Clin Infect Dis. 2004; 39(2):92-99. [PMID: 15306986 DOI: 10.1086/383269]
57. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J VascSurg. 2010; 52:37-43. [PMID: 20804932 DOI: 10.1016/j.jvs.2010.06.007]
58. Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg. 2004; 187:17-24 [PMID: 15147987 DOI: 10.1016/S0002-9610 (03)00297-6]
59. Rathur HM, Boulton AJ. Pathogenesis of foot ulcers and the need for offloading. HormMetab Res. 2005; 37(1):61-68 [PMID: 15918113 DOI: 10.1055/s-2005-861398]
60. Rathur HM, Boulton AJ. The diabetic foot. Clin Dermatol. 2007; 25:109-120 [PMID: 17276208 DOI: 10.1016/j. clindermat ol.2006.09.015]
61. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP, Drury DA *et al*. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care. 1989; 12:384-388 [PMID: 2659299]
62. Piaggesi A, Viacava P, Rizzo L, Naccarato G, Baccetti F, Romanelli M *et al*. Semiquantitative analysis of the histopathological features of the neuropathic foot ulcer: effects of pressure relief. Diabetes Care. 2003; 26:3123-3128 [PMID: 14578249 DOI: 10.2337/diacare.26.11. 3123]
63. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K *et al*. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med. 2008; 25:700-707 [PMID: 18544108 DOI: 10.1111/ j.1464-5491.2008.02445.x.]
64. Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care. 2008; 31:2118-2119 [PMID: 18694976 DOI: 10.2337/dc 08-0771]
65. Fife CE, Carter MJ, Walker D, Thomson B, Eckert KA. Diabetic foot ulcer off-loading: The gap between evidence and practice. Data from the US Wound Registry. Adv Skin Wound Care 2014; 27:310-316 [PMID: 24932951 DOI: 10.1097/01.ASW.0000450831. 65667.89]
66. DiPreta JA. Outpatient assessment and management of the diabetic foot. Med Clin North Am. 2014; 98:353-373 [PMID: 24559880 DOI: 10.1016/j.mcna.2013.10.010]
67. Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician. 2002; 66:1655-1662 [PMID: 12449264]
68. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH *et al*. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005; 28:555-559 [PMID: 15735187 DOI: 10.2337/ diacare.28.3.555]
69. Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care. 2005; 28:551-554 [PMID: 15735186 DOI: 10.2337/ diacare.28.3.551]
70. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005; 293:217-228 [PMID: 15644549 DOI: 10.1001/jama.293.2.217]
71. Clark RAF. Wound repair: overview and general considerations. In: Clark RAF, editor. The molecular and cellular basis of wound repair. New York: Plenum Press, 1996, 3-50.
72. Harding KG, Jones V, Price P. Topical treatment: which dressing to choose. Diabetes Metab Res Rev. 2000; 16(1):47-50.
73. Olson ME, Wright JB, Lam K, Burrell RE. Healing of porcine donor sites covered with silver-coated dressings. Eur J Surg. 2000; 166:486-9.
74. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment of burn wounds. J Burn Care Rehabil. 1998; 19:531-7.
75. Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. Arch Phys Med Rehabil. 2001; 82:721-725 [PMID: 11387573 DOI: 10. 1053/apmr.2001.23780]
76. Petrofsky JS, Lawson D, Berk L, Suh H. Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30 min three times per week. J Diabetes. 2010; 2:41-46 [PMID: 20923474 DOI: 10.1111 /j.1753-0407.2009.00058.x]
77. Lundeberg TC, Eriksson SV, Malm M. Electrical nerve stimulation improves healing of diabetic ulcers. Ann PlastSurg. 1992; 29:328-331 [PMID: 1466529]
78. Baker LL, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes Care. 1997; 20:405-412 [PMID: 9051395 DOI: 10.2337/diacare.20.3.405]
79. Thakral G, Lafontaine J, Najafi B, Talal TK, Kim P, Lavery LA. Electrical stimulation to accelerate wound healing. Diabet Foot Ankle, 2013, 4 [PMID: 24049559 DOI: 10.3402/dfa. v4i0.22081]
80. Barnes R, Shahin Y, Gohil R, Chetter I. Electrical stimulation vs. standard care for chronic ulcer healing: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Invest. 2014; 44:429-440 [PMID: 24456185 DOI: 10.1016/ j.ejvs.2008.06.010]
81. Papanas N, Maltezos E. Becaplermin gel in the treatment of diabetic neuropathic foot ulcers. ClinInterv Aging. 2008; 3:233-240 [PMID: 18686746]
82. Bennett SP, Griffiths GD, Schor AM, Leese GP, Schor SL. Growth factors in the treatment of diabetic foot ulcers. Br J Surg. 2003; 90:133-146 [PMID: 12555288 DOI: 10.1002/bjs.4019]
83. Wieman TJ. Clinical efficacy of becaplermin (rhPDGF-BB) gel. Becaplermin Gel Studies Group. Am J Surg. 1998; 176:74-79 [PMID: 9777976]
84. Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic non healing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986; 204:322-330 [PMID: 3753059 DOI: 10.1097/00000658-198609000-0 0011]
85. Steed DL. Clinical evaluation of recombinant human

platelet-derived growth factor for the treatment of lower extremity ulcers. PlastReconstrSurg. 2006; 117:143-149. Discussion 150S-151S [PMID: 16799381]
86. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen. 2008; 16:585-601 [PMID: 19128254 DOI: 10.1111/j.1524-475X.2008.00410.x]
87. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebocontrolled double-blind study. Diabetes Care. 1998; 21:822-827 [PMID: 9589248 DOI: 10.2337/diacare.21.5.822]
88. Sibbald RG, Torrance G, Hux M, Attard C, Milkovich N. Cost-effectiveness of becaplermin for nonhealing neuropathic diabetic foot ulcers. Ostomy Wound Manage. 2003; 49:76-84 [PMID: 14652415]
89. Hogge J, Krasner D, Nguyen H, Harkless LB, Armstrong DG. The potential benefits of advanced therapeutic modalities in the treatment of diabetic foot wounds. J Am Podiatr Med Assoc. 2000; 90:57-65 [PMID: 10697968 DOI: 10.7547/87507315-90-257]