Diabetic foot ulcer: A review

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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 [16-22]. (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-Meggitt 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.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lesion</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No open lesion: may have deformity or cellulitis</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>Superficial ulcer</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>1</td>
<td>Deep ulcer to tendon, or joint capsule</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>2</td>
<td>Deep ulcers with abscess, osteomyelitis, or joint sepsis</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>3</td>
<td>Localized gangrene — forefoot or heel</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>4</td>
<td>Gangrene of entire foot</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
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</tbody>
</table>

Table 2: Depth Ischemic classification System.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lesion</th>
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<tbody>
<tr>
<td>0</td>
<td>No open lesions: may have deformity or cellulitis</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>Superficial ulcer</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>1</td>
<td>Deep ulcer to tendon, or joint capsule</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
</tr>
<tr>
<td>2</td>
<td>Deep ulcers with abscess, osteomyelitis, or joint sepsis</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
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<td>3</td>
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<td>Gangrene of entire foot</td>
</tr>
<tr>
<td>A Ischemic</td>
<td>B Infected</td>
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</tbody>
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Table 3: University of Texas Classification System

<table>
<thead>
<tr>
<th>Stages</th>
<th>Grade</th>
<th>I.</th>
<th>II.</th>
<th>III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pre-or post-ulcerative lesions</td>
<td>Superficial wound not involving tendon capsule or bone</td>
<td>Wound penetrating to tendon or capsule</td>
<td>Wound penetrating to bone or joint</td>
</tr>
<tr>
<td>B</td>
<td>With infection</td>
<td>With infection</td>
<td>With infection</td>
<td>With infection</td>
</tr>
<tr>
<td>C</td>
<td>With ischemia</td>
<td>With ischemia</td>
<td>With ischemia</td>
<td>With ischemia</td>
</tr>
<tr>
<td>D</td>
<td>With infection and ischemia</td>
<td>With infection and ischemia</td>
<td>With infection and ischemia</td>
<td>With infection and ischemia</td>
</tr>
</tbody>
</table>

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
Ulcér 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 [49]. 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 contraindicated 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 as significantly higher proportion of people with DFU were healed after 12 wk wearing a TCC compared with the two other widely used offloading modalities [61]. 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 is dry 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 factor beta (PDGF-beta), transforming growth factor beta] 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, 72, 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 [79] 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**


15. 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
54. Game FL, Hincliffe RJ, Apelqvist J et al. A systematic review of interventions to enhance the healing of chronic


85. Steed DL. Clinical evaluation of recombinant human


