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Advanced Pharmacotherapy for Diabetic Foot Ulcer: An Overview

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ABSTRACT

"Diabetic foot ulcers are considered one of the major and serious complications of diabetes. The causes of diabetic foot ulcers vary, and include metabolic, vascular, neurological, and immunological causes. Diabetic foot ulcers can occur as a result of dryness, roughness, inflammation, microbial contamination, damage to foot tissues, and so on. This review discusses some of the important factors responsible for the development of diabetic wounds. Diabetic foot ulcers are a common complication of diabetes, with their annual incidence ranging between 9.1 and 26.1 million cases worldwide. In addition to medications such as insulin, metformin, thiazolidinediones, sulfonylureas, and DPP-4 inhibitors, which lower blood sugar levels, these drugs have also demonstrated effectiveness in treating chronic wounds due to their anti-inflammatory properties. Oral antibiotics, such as clindamycin, amoxicillin-clavulanic acid, moxifloxacin, and cephalexin, are often prescribed to treat microbial infections. To accelerate wound healing, various auxiliary dressing materials are used, such as hydrocolloid, hydrogel, foam, alginate, iodine preparation, and silver-impregnated dressings. Emerging treatments include maggot therapy, hyperbaric oxygen therapy (HBOT), negative pressure wound therapy (NPWT), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factors (IGF1, IGF2), epidermal growth factor (EGF), and stem cell therapy. These therapies are used to address impaired wound healing in diabetic patients."

Keywords: Diabetic Foot Ulcers, Pharmacological Treatment, Antibiotics, Growth Factors, Hydrogels, Stem Cell Therapy

INTRODUCTION

Diabetes mellitus (DM) is a group of physiological dysfunctions caused by hyperglycemia resulting directly from insulin resistance, insufficient insulin production, or excessive glucagon production [1]. It has several subclassifications, including Type 1 Diabetes Mellitus (T1DM) or Insulin-Dependent, Type 2 Diabetes Mellitus (T2DM) or Non-Insulin-Dependent, Maturity-Onset Diabetes of the Young (MODY), gestational diabetes, neonatal diabetes, and secondary forms resulting from endocrinopathies, steroid use, etc.

Type 1 diabetes typically affects children or adolescents due to autoimmune destruction of the pancreatic islet β-cells, while Type 2 diabetes primarily affects middle-aged and older adults who have prolonged hyperglycemia from poor dietary and lifestyle choices and impaired insulin secretion. MODY is diagnosed at an early age (often under 25 years) and results in non-insulin-dependent diabetes. Pregnancy-related diabetes is primarily known as gestational diabetes. Although the exact cause of its development is still unknown, some researchers suspect that HLA antigens—especially HLA-DR2, 3, and 4—may be involved [2–4].

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An ancient Egyptian description from 3,000 years ago indicated symptoms comparable to diabetes mellitus. Indian physicians called it *madhumeha* ("honey urine") because it attracted ants. Type 1 and Type 2 diabetes were later named after the ancient Indian physicians Sushruta and Charaka (400–500 A.D.), who were able to identify and differentiate between the two forms of the disease [5]. Aretaeus of Cappadocia is credited with coining the term "diabetes" (81–133 A.D.). Later, Thomas Willis coined the word *mellitus*, meaning "honey-sweet," in 1675 after rediscovering the sweetness of urine and blood in affected patients [6].

Diabetic foot ulcer is one of the most common and devastating complications of diabetes mellitus. It is characterized as an ulcerated foot in a diabetic patient associated with peripheral artery disease, neuropathy, or both conditions affecting the lower limb. The three main risk factors for developing foot ulcers are peripheral artery disease, diabetic neuropathy, and consequent foot trauma [7].

Diabetic Foot Ulcer (DFU)

The vague and imprecise nature of this concept is partially reflected in the practical guidelines developed by the International Working Group on the Diabetic Foot (IWGDF), which defines DFU as a set of symptoms secondary to current or previous diabetes, including skin chapping, ulceration, infection, or destruction of foot tissue [8].

Types of diabetic foot ulcers:

Diabetic foot ulcers can be classified into different types based on their characteristics and underlying causes, including [9]:

1. Neuropathic ulcers:

Diabetic neuropathy is one of the long-term consequences of the disease. It affects the touch, temperature, and pain-sensing nerves, particularly those in the legs and feet. Because there is no sensation around pressure points, neuropathic ulcers develop as a result of trauma or pressure that goes unnoticed. At these locations, calluses may develop to such a thickness that they traumatize surrounding tissue and result in ulceration. Furthermore, minor cuts and scrapes may go unnoticed and untreated, which can lead to the development of ulcers.

Pressure points on the foot—such as the tips of the toes, the area beneath the big toe, and the sides and heel—are common sites for neuropathic ulcers. These ulcers typically appear with thick calluses surrounding them. The amount of trauma the skin has endured determines the depth of the wound [10–12].

2. Ischemic ulcers:

Ischemia refers to reduced blood flow to a specific area of the body. Insufficient blood flow to the legs and feet damages tissue and results in cell death. Peripheral artery disease (PAD), an abnormal narrowing of the arteries that causes inadequate blood flow, is the primary cause of ischemic ulcers. These diabetic ulcers deteriorate quickly and heal slowly.

Ischemic ulcers frequently occur on the toes, heels, and edges of the foot. They often appear as shallow, pink, open lesions surrounded by pale tissue. The ulcer may develop a black necrotic scab if it has dried out [13–16].

3. Neuroischemic ulcers:

Individuals with both peripheral neuropathy and ischemia from peripheral artery disease are at risk for developing neuroischemic ulcers. If infected, these ulcers have a high risk of amputation and are the least likely to heal on their own. This combination is common in advanced cases of diabetic foot complications.

Neuroischemic ulcers exhibit features of both neuropathic and ischemic ulcers, including reduced sensation, poor blood flow, and a high potential for severe complications. They commonly occur on the toes, the edges of the foot, and the dorsum of the foot—the portion that faces upward when standing. Neuroischemic ulcers can also form under excessively thick toenails and on the tips of the toes. Their appearance typically includes pale or yellow-colored tissue with a thin layer of callused, glassy

skin surrounding it. Raised margins may also be present around the wound [17–19].

4. Malignant (Neoplastic) ulcers

Malignant ulcers often arise in the context of long-standing, non-healing wounds. Chronic wounds provide an environment conducive to the development of cancer, and squamous cell carcinoma is a type of cancer commonly associated with chronic wounds. Factors contributing to the growth of malignant ulcers in people with diabetes may include prolonged exposure to inflammation, repeated trauma, and impaired immune function. The presence of chronic wounds and associated tissue changes creates an environment conducive to cancer development. Malignant ulcers may exhibit characteristics that differ from typical DFU. Signs of malignancy may include irregular borders, rapid growth, changes in color, and the presence of nodules or masses within the ulcerated area [20–23].

5. Traumatic ulcers:

Traumatic ulcers in the context of DF complications refer to ulcers that result from external injuries or trauma. These injuries often go unnoticed, especially in individuals with diabetic neuropathy, as they may have reduced or absent sensation in their feet. Traumatic ulcers can be caused by various external factors, including ill-fitting shoes, friction, pressure, burns, cuts, or foreign objects such as stones or sharp materials that can injure the toes, sides of the feet, and the bottom of the foot. While similar to neuropathic ulcers, traumatic ulcers are specifically linked to identifiable external factors. Traumatic ulcers can be a significant concern because the lack of pain perception may delay the identification and treatment of the injury, leading to the development of long-lasting wounds [18, 24–25].

6. Postoperative ulcers:

Postoperative ulcers in the context of DF complications refer to ulcers that develop at or near surgical sites following foot or lower extremity surgeries in individuals with diabetes. While surgery is often necessary to address various foot-related issues, including the correction of deformities, removal of bone spurs, or treatment of infections, there is a risk of complications such as postoperative ulcers due to poor wound healing. These ulcers occur following surgical procedures and are often related to factors such as infection, inadequate blood supply, or delayed wound healing [26].

Prevalence of diabetic wound:

Worldwide, diabetic complications—particularly diabetic foot ulcers—affect approximately 9.1 to 26.1 million people every year. Between 15% and 25% of individuals with diabetes mellitus will develop a diabetic wound at some point in their lives. There is no doubt that the annual increase in the number of DFU diagnoses will coincide with an increase in disease burden. People aged 45 and older with diabetes are more likely to develop diabetic ulcers, although they can occur at any age. In the United States, Native Americans, African Americans, and Latinos are the groups most likely to develop foot ulcers [27].

The yearly prevalence of foot ulcers in individuals with diabetes ranges from 4.0% to 9.1%. The incidence is higher in people who have developed neuropathy, estimated at 5.0% to 7.5% [28]. Recent estimates indicate that 60% to 80% of these ulcers can cure, 10% to 15% heal, and 5% to 24% eventually result in limb amputation (Figure 1). Males (4.5%) are more likely than females (3.5%) to develop diabetic foot ulcers, and individuals with type 2 diabetes (6.4%) are more likely to develop DFU than those with type 1 diabetes (5.5%), according to a systematic meta-analysis.

Approximately 77 million people in India have diabetes; by 2045, this number is predicted to rise to 135.7 million, making it one of the most affected nations. In India, 8.9% of people have diabetes, and the disease is estimated to cause one million diabetes-related deaths annually. According to estimates by Shankhdhar et al. [30] and Singh et al. [31], around 25% of Indian diabetes patients will experience DFU. Consequently, it is necessary to explore the potential etiological and epidemiological variations in diabetes-related

complications, including DFU. The increasing incidence of diabetes is currently linked to a rise in DFU-related issues in India. A number of variables, such as lifestyle and socioeconomic status, influence the prevalence of DFU in India. Furthermore, the demographic and etiological trends of DFU have been examined from an Indian perspective.

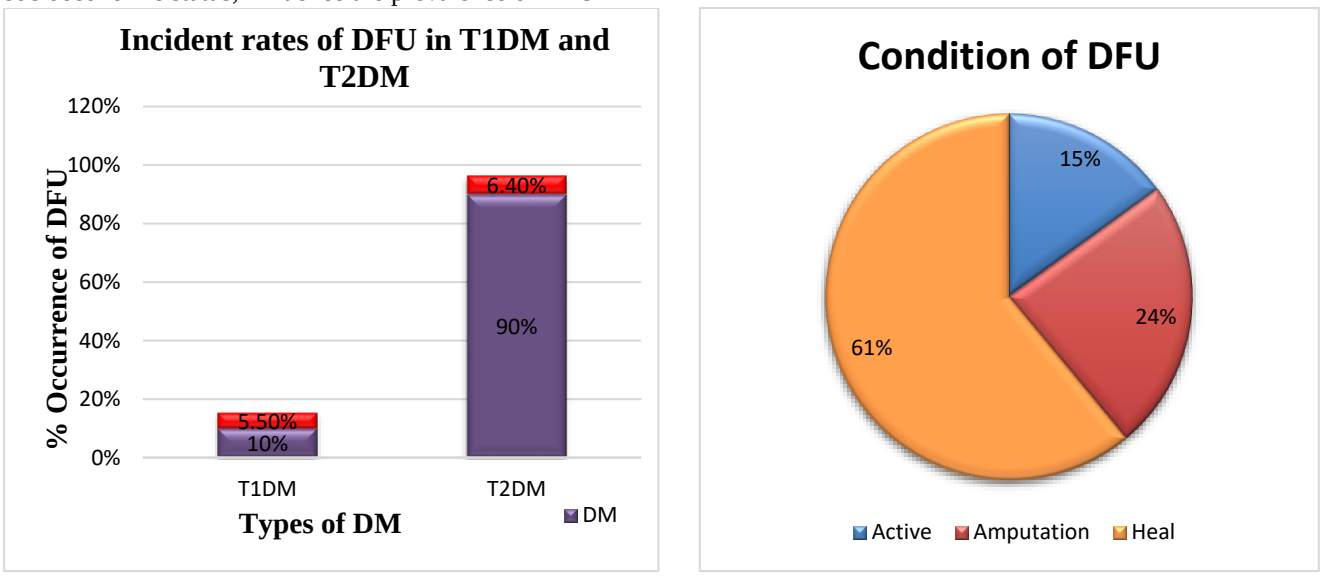

Figure 1. (A) Graphical representation of incident rates of DFU in T1DM and T2DM, and (B) graphical representation of condition of Diabetic Foot Ulcers (DFU) in India.

Etiology of Diabetic Foot Ulcers:

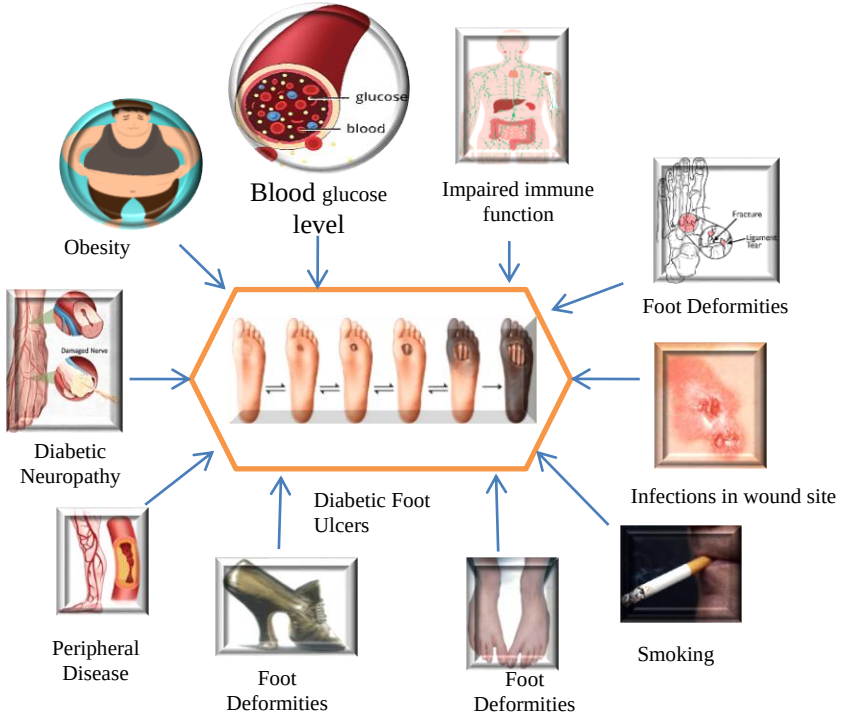

Figure 2 diagrammatic representation of etiology of Diabetic Foot Ulcers.

The etiology of DFU is multifactorial, involving a combination of metabolic, vascular, neuropathic, and immunologic factors. Here are some key factors that cause diabetic foot ulcers (Figure 2) [33–37]:

1. **Neuropathy:** Diabetic neuropathy, particularly peripheral neuropathy, is a key risk factor for DFUs. Neuropathy affects the nerves in the feet, leading to reduced sensation and impaired pain perception. Patients with neuropathy may not feel injuries or pressure on their feet, allowing minor injuries to go unnoticed and progress to ulcers.
2. **Peripheral Artery Disease (PAD):** Diabetes can lead to atherosclerosis, a condition in which blood vessels become narrowed or blocked. PAD reduces blood flow to the extremities, impairing wound healing and making individuals more prone to infections.
3. **Foot deformities:** Structural abnormalities of the foot, such as hammertoes, bunions, and Charcot foot deformity—a disorder marked by abnormalities of bones and joints—can exacerbate pressure points and lead to ulcer formation.
4. **Impaired immune function:** People with diabetes have a weakened immune system, which increases their susceptibility to infection. Chronic wounds may result from the impaired immune response of ulcers, making it more difficult for the body to fight off infections.
5. **Poor glycemic control:** Uncontrolled blood glucose levels can negatively impact wound healing. Excessive blood glucose can hinder angiogenesis (the formation of new blood vessels), damage white blood cells, and delay the healing process in general.
6. **Inadequate footwear:** People with neuropathy are particularly susceptible to developing ulcers due to wearing inappropriate or ill-fitting shoes. Shoes that do not provide enough support or that generate friction or pressure points can damage the skin.
7. **Smoking:** It is well known that smoking increases the risk of poor circulation and delayed wound healing. Smokers with diabetes have an increased chance of developing complications such as DFUs.
8. **Obesity:** Excess body weight can exacerbate mechanical stress on the foot and raise the incidence of ulcers. Furthermore, obesity is associated with insulin resistance and inflammation.
9. **Foot trauma:** Reduced sensation and impaired awareness of the feet increase the likelihood of injuries going unnoticed. Simple trauma such as cuts, blisters, or calluses can develop into ulcers if not properly managed.
10. **Infections:** People with diabetes are more prone to infections once an ulcer develops because of their weakened immune system and reduced blood flow, both of which can delay the healing process.

A multidisciplinary strategy is necessary to manage diabetic foot ulcers. This approach entails proper wound care, infection management, glucose control, vascular assessment, and patient education on foot care. The risk of diabetic foot ulcers can be reduced by adopting preventive measures such as routine foot examinations, suitable footwear, and lifestyle changes.

Classification system for diagnosis or assessing DFU

The National Institute for Clinical Excellence recommends that all patients with diabetes undergo a yearly evaluation of their diabetic foot.

- **Neurological foot testing:** 10 g monofilament applied to four different points on each foot, along with one of the following tests: vibration perception threshold, ankle reflexes, pinprick sensation, or vibration using a 128 Hz tuning fork.

- **Foot shape:** Presence of prominent metatarsal heads, claw toes, hallux valgus, muscle wasting, or Charcot deformity.
- **Dermatological:** Callus, erythema, and sweating.
- **Vascular:** Foot pulses, ankle–brachial index, and Doppler wave patterns [38].

DFU represents a broad range of illness severity and acuity. Important characteristics considered when evaluating DFU include wound location, depth, size, severity of infection, and the presence of pressure ulcers or PAD. The goals of a classification system are to standardize the assessment of wounds, communicate information about the patient and the wound between healthcare practitioners over time, guide clinical decision-making and prognostication, and enable research on interventions and outcomes that may be broadly applied.

Although DFU is commonly classified using a number of schemas (Table 2), there is no single accepted gold standard. The choice of classification system depends on several factors, including the patient population, practice environment, available resources, and intended use [39].

Wagnere Meggitt system

Wagner (1981) created a classification system (Table 1) in the 1970s. This method evaluates the extent of the ulcer and whether gangrene or osteomyelitis is present. Six grades, from 0 to 5, were originally assigned to lesions; however, grade 0 (which denotes unbroken skin) is rarely applied in clinical settings.

The physical depth of the lesion in and through the soft tissues of the foot determines the first three ulcer grades (1 to 3). Wagner assigns grades 4 and 5 according to the severity of foot gangrene. The most recent evaluations make it evident that not all DFUs and related conditions are sufficiently addressed by Wagner's system. Only grade 3 suggests infection, and even then, only indirectly. The system has limited ability to recognize and characterize vascular disease as a separate risk factor for poor outcomes, even when used as a surgical tool.

Moreover, this system cannot distinguish between superficial wounds with a vascular component and those that are infected but do not develop gangrene. For these reasons, the 2015 guideline from the National Institute for Health and Care Excellence (NICE) does not recommend using the Wagner classification system to assess DFU [40–41].

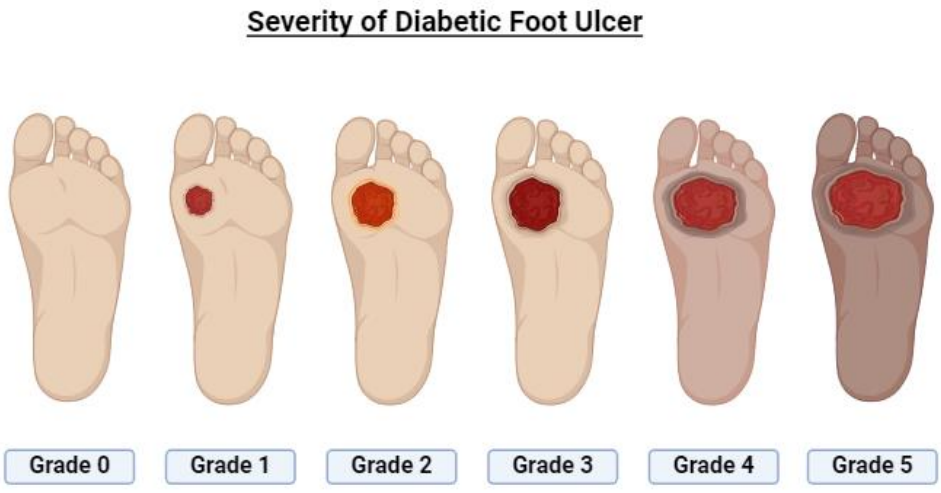

Figure 3. diagrammatic representation of the Severity Diabetic Foot Ulcer according to Meggitt-Wagner system

Table 1 Meggitt-Wagner system

No.	Grade	Feature
1	Grade 0	Intact skin (There is no ulcer or any symptoms other than pain)
2	Grade 1	Superficial wound/ ulcer
3	Grade 2	Deep ulcer affecting the capsule, ligament and tendon
4	Grade 3	Ulcer that affects the bone
5	Grade 4	Formation of gangrene* on fore foot
6	Grade 5	Gangrene affecting the entire foot, including more than two thirds of foot

Note – Gangrene* - Destruction of the foot's part due to poor supply or extensive infection

Table 2 Different classification system for diagnosis or assessing DFU

S. No.	System	Components	Benefits	Limitation	Rf.
1	Wagner (Meggitt-Wagner)	Based on the depth and length of the wound as well as existence of infection, ulcers are rated on a scale of zero to five, representing pre-or post-ulcerative lesions free of infection to serve wounds with complete foot gangrene.	Easy being the first to be extensively used, it enables historical data comparison.	High score indicates LEA differential interrater dependability excludes PN/LOPS and perfusion.	43
2	University of Texas (UT)	Grades ulcers (0–3) according to their depth and classifies them into stages (A–D) based on the presence of ischemia (C), infection (B), or both (D).	Easy exceptional at catching lesion before and after ulceration highest level and grade indicate LEA only.	Somewhat reliable inter-rater agreement; dichotomized ischemia is not very specific. The system also excludes PN/LOPS and ulcer size.	44-45

S. No.	System	Components	Benefits	Limitation	Rf.
3	Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI)	Offers multimodal limb risk assessment based on wound size and depth (w), ischemia (I), and foot infection presence and severity (fI), all on scale with specific objective criteria for each category. Determines a clinical stage that estimates the risk of amputation from 1 (very low) to 4 (very high) based on the combination of these factors (stage 5: unsalvageable limb) is assigned.	Exceptionally good inter-rater dependability has been demonstrated, and infection levels are thoroughly verified according to IWGDF criteria. This system is intended to offer therapeutic guidance regarding the anticipated benefits of revascularization and is predictive of functional status, healing duration, and the risk of LEA.	Comparatively intricate needs knowledge of perfusion measurements does not include PN/LOPS.	46
4	Perfusion extent/size, depth/ tissue loss, infection, and sensation (PEDIS)	Developed to standardize prospective clinical research by the IWGDP. Includes grade information for the following categories: perfusion, extent/size, infection and sensation, all of which are categorized in a stratified manner.	Extensively validated in a variety of contexts where data may be scarce, this system is unique in its inclusion of ulcer location. Higher ratings are indicative of recovery, and the tool has several applications in population-based research, particularly in resource-limited environments.	Dichotomized factors make it difficult to evaluate how severe aspects, such as severe ischemia or infection, contribute relative to one another or how much they vary over time.	47
5	Site, ischemia, neuropathy, bacterial infection, area and depth (SINBAD)	Intended for use in population-based audits, it assigns a rating of 1 (present) or 0 (absent) for ulcer location, ischemia, peripheral neuropathy, infection, area, and depth.	Extensively verified in a variety of contexts, its inclusion of ulcer location makes it unique. Higher ratings are indicative of recovery, and it has a wide range of uses in settings with limited resources where data may be scarce.	Dichotomized factors to evaluate how severe aspects, such as severe ischemia to one another or how much they vary over time.	48

Note: IWGDF- International Working Group of DF; LEA- Lover-Extremity Amputation; LOPS- Loss o Protective Sensation.

Pathophysiology of DFU

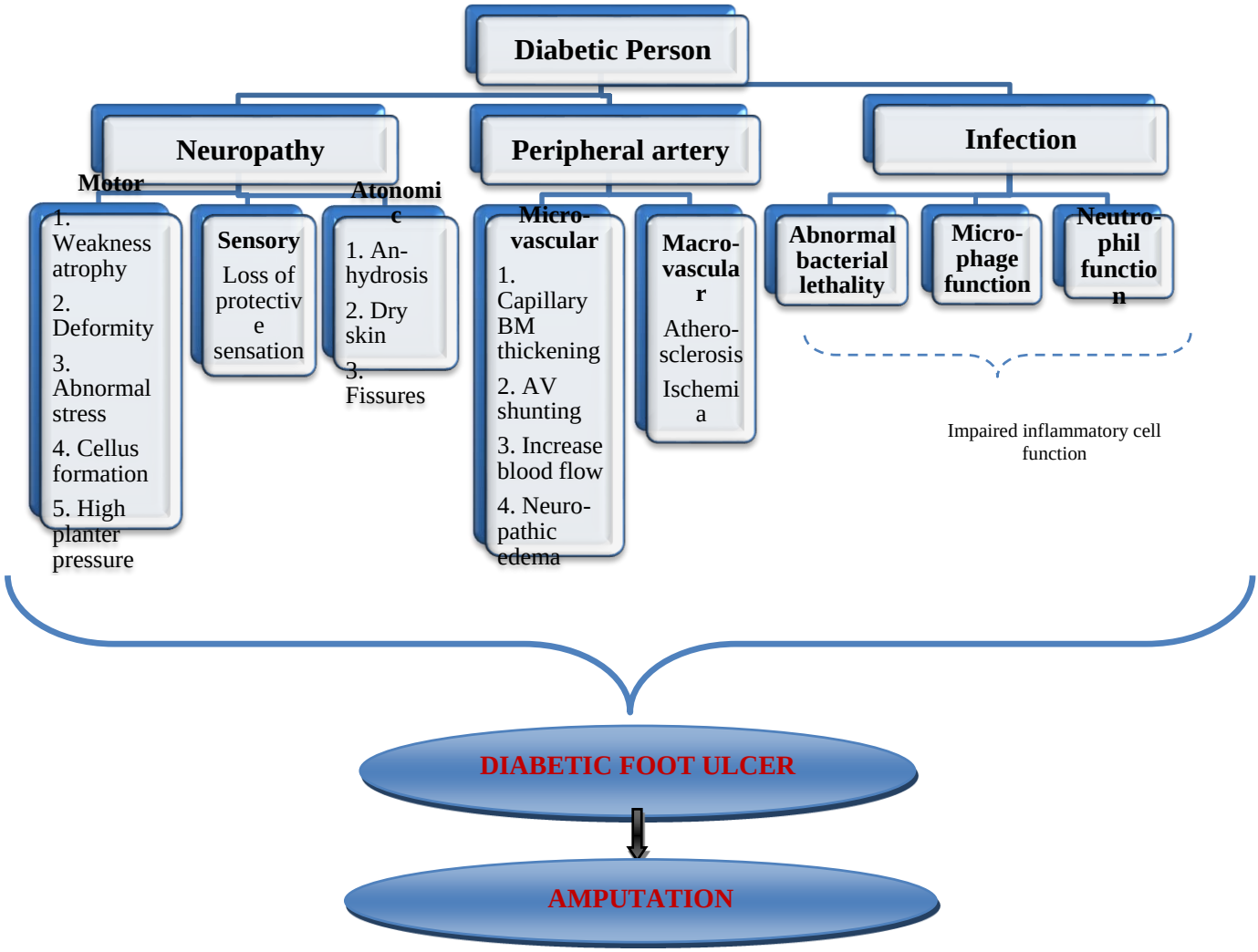

Figure 4: Diagrammatic representation of pathophysiology of diabetic foot ulcer.

A diabetic ulcer typically progresses through three stages. The initial step is the process of a callus developing. The cause of the callus is neuropathy. Foot deformities are caused by motor neuropathy, while sensory neuropathy results in sensory loss, which leads to ongoing trauma. Autonomic neuropathy is another factor that contributes to dry skin. Subcutaneous bleeding ultimately results from persistent injury to the callus, which wears down and becomes an ulcer. Patients with diabetes mellitus may also experience widespread atherosclerosis of small blood vessels in their feet and legs, which can lead to diabetic foot infection. Vascular compromise results

from this disease. Because blood cannot reach the wound, it takes longer to heal and eventually becomes necrotic and progresses to gangrene [36].

Patients with diabetes mellitus (DM) are more likely to develop DFU, mostly as a result of peripheral neuropathy, peripheral vascular dysfunction, and a weakened immunological response. Moreover, DM is linked to a wound-healing issue that increases the chance of infection. In diabetes mellitus, neuropathy affects the motor, sensory, and autonomic systems. Damage to the leg muscles' innervation causes an imbalance between flexion and extension of the leg, which leads to deformity and a shift in pressure points. Eventually, this causes damage to the skin that develops into ulcers. Autonomic neuropathy causes a decrease in oil gland activity and sweating, which increases the risk of injury and lowers the moisture content of the foot. Because sensory neuropathy decreases the pain threshold, the wound is frequently not noticed until it becomes worse.

Hyperglycemia causes constriction of peripheral arteries as a result of decreased endothelial synthesis of vasodilators, vascular smooth muscle dysfunction, and endothelial dysfunction. In diabetes mellitus, hyperglycemia elevates the levels of the vasoconstrictor thromboxane A_2, which aggregates platelets and raises the risk of plasma hypercoagulability. Hypertension and dyslipidemia also have an impact on peripheral artery disease. Occlusive arterial disease, which is further brought on by peripheral arterial narrowing, increases the risk of ulcers and lower extremity ischemia. The resulting lesions are prone to infection, can progress to gangrene, and eventually necessitate lower-limb or below-knee amputation [49].

In individuals with diabetes mellitus, the capacity of peripheral soft tissue to heal is decreased, which leads to ulcers. When diabetes reaches an advanced stage, blood glucose control is no longer enough to reverse the structural damage to skin tissue, neurons, blood vessels, and other supporting tissues. Wound complications are likely to occur in diabetic wound healing, which further delays healing. Gangrene, septicemia, and infections such as cellulitis, abscesses, and osteomyelitis are some of these adverse effects [37,50].

Diabetic foot infections can range in severity from straightforward cellulitis to potentially lethal necrotizing fasciitis that puts limbs at risk. Inadequate blood sugar management over time can cause immunologic dysfunction, resulting in reduced leukocyte and complement activity and increased development of invasive tissue infections. Injuries or poor perfusion of the skin and soft tissue can allow bacteria to quickly penetrate deep into fascia, which can lead to sepsis and a potentially fatal infection. Antibiotic-resistant bacterial strains and polymicrobial infections, such as Methicillin-Resistant *Staphylococcus aureus* (MRSA), which is seen in 30–40% of cases, are common. These include gram-negative bacteria such as *E. coli*, staphylococci, streptococci, and enterococci. When resistant bacterial strains—often the result of prolonged or repeated antibiotic usage—are involved in the diabetic foot infection, the risk of amputation increases. About one-third of patients have gas-forming infections, which are caused by *Clostridial* species or by a combination of *E. coli* and anaerobic streptococcal infections [51].

Wound healing process in diabetic mellitus [52-57]

Just like any other wound, a diabetic foot ulcer starts out normally. It may begin as a minor injury such as a cut, scrape, blister, etc. Such wounds cannot heal normally due to problems associated with poorly controlled diabetes, such as impaired circulation and nerve damage. Instead, the skin breaks down further, making deeper tissue layers more vulnerable to infection and microorganisms.

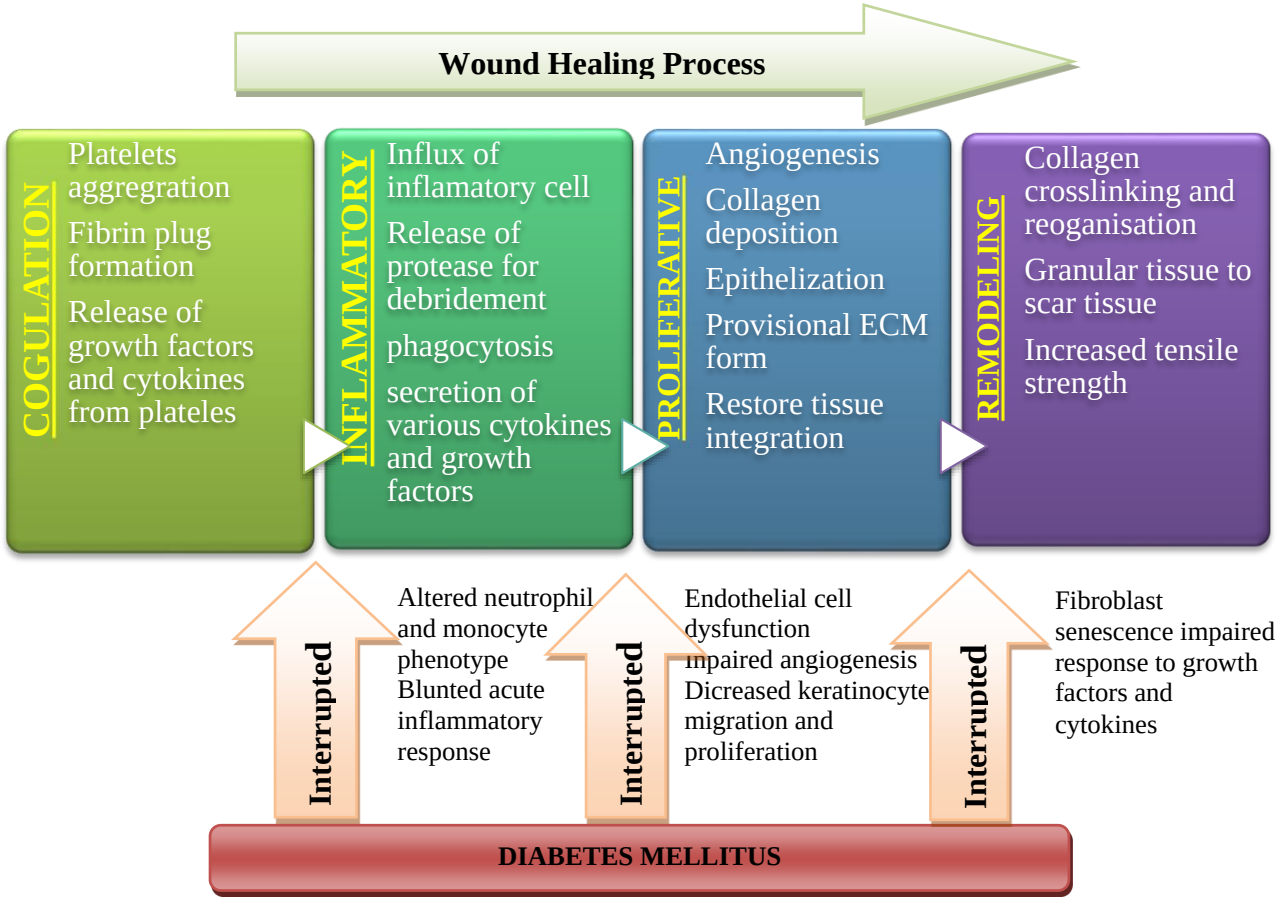

Figure 4. Diagrammatic representation of interruption of diabetic mellitus in normal wound healing process

A major problem is that diabetic wounds do not heal in accordance with the standard dynamic wound-healing process, which is comprised of four phases: hemostasis, inflammation, proliferation, and remodeling (Figure 4).

1. The Hemostasis

During the initial phase of cell repair, platelets need to be activated, aggregate, and adhere to the wounded endothelium in order to maintain hemostasis, also referred to as coagulation. Once this process is initiated, fibrinogen converts to fibrin, which forms the temporary extracellular matrix (ECM) and the thrombus. Activated platelets, neutrophils, and monocytes are among the cells involved. Growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β), are released by these cells. Reduced fibrinolysis and hypercoagulability, compared with normal individuals, are hemostasis-phase abnormalities observed in DM patients.

2. Inflammation

Because neutrophils, macrophages, and mast cells produce growth factors such as PDGF, epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1), as well as inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), an inflammatory process occurs when tissue injury happens. The wound-healing process depends on these growth factors. In diabetes mellitus, there

is a disturbance in the equilibrium of these cytokines, leading to modified wound healing. There is evidence that neutrophils release cytokines differently and function less effectively, which raises the risk of wound infection.

3. Proliferation and Migration

When inflammation decreases, several processes take place at the lesion site: extracellular matrix (ECM) proteins such as collagen, fibronectin, and vitronectin develop; wound contraction occurs; and angiogenesis ensues to restore oxygen supply. The migration of keratinocytes and cell mobility depend on these proteins. Each of these stages must be completed by the tissue in order for it to regain its integrity and functionality. Atypical cell migration is the cause of the diabetic wound's insufficient re-epithelialization, which impedes the healing process. Additionally, reports indicate reduced angiogenesis and, consequently, reduced blood flow in patients with diabetes mellitus.

4. Remodeling phase

This phase, which starts approximately a week after the incision closes, can last beyond six months. In this stage, more collagen is produced than is degraded, replacing the transient extracellular matrix that fibrin and fibronectin initially produced. A scar forms as this granulation tissue matures into scar tissue that increases the wound's resistance.

Anatomic integrity and comparable function are restored as a result of the complex and dynamic process of wound healing. Completing wound healing quickly and effectively while preventing the spread of infection and sepsis is essential for wound management.

Prevention and management of diabetes foot ulcer complications [58-59]

Diabetes is a long-term metabolic illness that has a significant impact on the body's vascular system. Treatment for the metabolic consequences of diabetes mellitus (DM) should be concurrent, with no preference for treating one metabolic issue over another. Target levels should be maintained below the suggested threshold, and metabolic disorders attributable to diabetes mellitus should be managed. Therefore, as the primary causes of DFU are neuropathy and PAD, preventive interventions should be implemented.

The following are the preventive steps and diabetic complication-management strategies:

- **Lifestyle modification:** Engaging in regular physical activity lowers the risk of problems by enhancing circulation and assisting in blood sugar regulation.
- **Keep a well diet:** Eating a well-balanced diet helps control blood sugar levels and provides the body with the vitamins and minerals needed to accelerate the healing process. Sufficient protein, carbohydrates, and vitamin C strengthen your defenses. Consult a dietician who specializes in diabetes for advice on the best diet.
- **Maintain Blood pressure:** Evaluate arterial blood flow and peripheral circulation on a regular basis. A sufficient blood supply is necessary for wound healing.
- **Glycaemic control:** To lower the risk of complications, maintain ideal blood glucose levels. It is crucial to follow a diabetes treatment strategy and perform routine monitoring.
- **Age, gender and length of diabetes**: The risk of ulcers and amputation rises two to four times with increasing duration of diabetes and age.
- **Smoking cessation:** Quitting smoking benefits overall health and circulation. Smokers with diabetes should be advised to stop, as smoking impedes wound healing and circulation.
- **Foot nail and skin care**
- **Fresh dressing:** Changing wound dressings regularly helps maintain their protective effect against infections. Dressings also maintain moisture in the wound, which is critical because moist wounds heal more quickly than dry ones. Moisture also accelerates the creation of new cells.
- **Skin moisturization:** Maintain a healthy level of moisture in your skin to avoid dryness and cracking, which can result in open sores.

- **Regular podiatric assessment:** Identifying a wound early helps prevent infections that could develop into more significant issues. Check your feet daily for new wounds and abnormalities, particularly if you have diabetic neuropathy.
- **Avoid pressure on foot:** Pressure restricts blood flow, which slows healing. Wear comfortable, well-fitting shoes to reduce pressure points, lower the risk of trauma or friction sores, and prevent ulcers.
- **Debridement:** Dead cells in and around a wound promote bacterial growth and worsen infection. Excessive dead tissue may also make it difficult to assess the extent of the wound. Therefore, when necessary, debridement—a medical procedure that removes dead, damaged, or contaminated tissue—is performed to enhance healing. Debridement is required only if the wound is not healing properly on its own.

Treatment of diabetic foot ulcers

One method for treating people with DFUs is to use a multidisciplinary approach and address the various processes involved in the condition. Multidisciplinary teams (MDTs) that include all relevant specialties (e.g., the departments of vascular surgery, endocrinology, plastic surgery, nursing, and orthopaedics) have been demonstrated to improve patient outcomes through cost reduction, a 50–85% reduction in the risk of DFUs and amputation, and enhancement of patient quality of life [60]. Appropriate categorization of DFU stage and severity is crucial for effective therapy. Proper care for DFUs should prioritize DM management in addition to wound care, efficient infection control, pressure reduction, and blood-flow optimization. The fundamental objectives of basic care for the management and treatment of DFUs are debridement, pressure reduction, infection control, and adequate perfusion [61–62]. The other techniques for management or treatment of DFU are as follows:

1. Antidiabetic drugs

Fascinatingly, a number of drugs commonly prescribed to treat diabetes, including insulin, metformin, thiazolidinediones, some sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors, have shown a variety of diverse effects in addition to anti-inflammatory properties that may help with the management of chronic wounds. These medications have been demonstrated to have favorable effects on MMP reduction, keratinocyte and fibroblast proliferation, angiogenesis, granulation tissue formation, and polarization toward a healing-promoting macrophage phenotype. However, whether this is clinically associated with improved wound healing under particular circumstances still needs to be demonstrated [63–65]. Regardless of cholesterol levels, the two most crucial strategies are quitting smoking and using medications such as antiplatelet agents and nicotine replacement therapy [66].

2. Treatments For Diabetic Peripheral Neuropathy (DPN)

As a result of the loss of sensation in the affected limbs, diabetic peripheral neuropathy (DPN) patients are more susceptible to trauma and are at increased risk of developing a diabetic foot ulcer [67]. Tight glycemic control is the first and most crucial step in DPN therapy. The most effective method for restoring normoglycemia is a pancreatic transplant. Several studies have demonstrated that motor and sensory neuropathy improved in DPN patients undergoing pancreas transplant therapy. However, the timing of the response varies [68–69]. Only three drugs have been approved by the FDA to treat pain associated with DPN: duloxetine, tapentadol, and pregabalin. When a patient has severe DPN and exhibits symptoms like numbness, burning, stabbing, or excruciating or unmanageable pain, pharmaceutical treatment is used [70]. Analgesics such as tramadol, acetaminophen, and certain opioids like oxycodone—which can be overused and cause nausea and constipation—are additional medicinal treatments available. Antidepressant medications such as venlafaxine, nortriptyline, and amitriptyline have been effective in treating neuropathic pain. They affect serotonin and noradrenaline reuptake as well as muscarinic

activity. Despite this, there are not many studies evaluating these drugs because real-world situations do not typically replicate the dosages used in scientific trials [71–72]. As a potential DPN treatment, therapies based on the use of mesenchymal stem cells (MSC) produced from adipose tissue are now being investigated. Biological therapy may be a helpful treatment for DPN since it increases blood flow, lowers chronic inflammation, and regenerates peripheral nerve fibers. Biological therapy uses low concentrations of IL-6 [73].

3. Treatments for peripheral arterial disease (Ischemia)

Diabetic patients with ischemia can be treated with revascularization of at least one foot artery to restore blood flow. This can be done if the toe pressure is less than 30 mmHg, or transcutaneous oxygen pressure ($TcPO_2$) is less than 25 mmHg, as well as in patients whose DFU does not heal with ankle pressure less than 50 mmHg or ankle-brachial index (ABI) less than 0.5. Ischemia in diabetic patients is due to a reduction of blood flow that can occur in both small and large vessels, including capillaries, arteries, and veins, or due to a decrease in angiogenesis [74]. First-line treatments include open bypass or endovascular revascularization techniques. In cases of long-term occlusion of the femoral-popliteal and infra-popliteal vessels, or obstruction of the common femoral artery and its bifurcation, a bypass is usually more successful and ensures extended patency. Nonetheless, in centers with significant expertise, conducting angioplasty is an alternative treatment for PAD. This involves inserting and inflating a small balloon into a restricted region of an artery to enhance blood flow. To be effective, this technique must be carried out on a patent distal vessel. Another treatment is atherectomy, which involves removing the atheroma with a rotating cutting blade. However, there is no evidence to support the superiority of atherectomy over angioplasty in any outcome.

Once any of the aforementioned procedures are completed, the patient needs multidisciplinary care to ensure that the treatment is effective. This includes pharmacological treatment for hypertension, hypercholesterolemia, and complications such as hemorrhage [75–77].

4. Wound dressing

Dressing promotes the absorption of exudates around the ulcer site while also providing an outer barrier and protection against external pressure and contaminants, thereby speeding up ulcer healing. Wound dressing can be passive, active, or interactive. Passive dressing is employed for the quantity of exudates while providing adequate protection [78]. Active and interactive dressings can change the physiology of the wound by increasing cellular activity and growth factor release. The primary types of dressing used for DFU are as follows: hydrocolloids, hydrogels, foams, alginates, iodine preparations, and silver-impregnated dressings, as well as approaches for expediting wound healing, which are becoming increasingly advanced [79]. Bandages and other non-adherent therapies are frequently utilized on diabetic wounds. Hydrogels and other specialized dressings are still being developed. According to Zhao et al. [80], hydrogel mixed with fibroblasts and insulin as bioactive dressings offers promising potential for treating diabetic foot ulcers (DFUs) by promoting neovascularization, collagen deposition, and wound healing. Regarding advancements in wound dressing technology, there is little evidence to support the concept that moist dressings are more effective than "dry" dressings, or vice versa. Randomized controlled trials have found that dressings impregnated with silver are no more effective in treating diabetic foot ulcers than dressings used for other forms of wounds [81].

5. Debridement

Debridement refers to the removal of infected or necrotic tissue from within or near a wound. Typically, this is done in concert with other local therapies to improve moisture balance and restrict bacterial growth. Debridement can be achieved chemically (with autolytic agents such as alginates, films, foams, hydrocolloids, and

hydrogels), mechanically (drying dead tissue with saltwater and then removing it), or medically (cutting dead tissue away from the wound) [82]. Surgical debridement is performed in a sterile environment using local anesthesia to remove necrotic tissue. Following the debridement procedure, the wound bed is properly prepared to support the growth of healthy granulation tissue [83].

The following are some advantages of debridement:

- Allowing medical professionals to view the whole wound.
- Removing dead tissue and draining exudate-fluid, cells, and cellular debris from blood vessels can lower the risk of infection.
- Deep swabs can be taken from living tissue.
- Promoting recovery and converting chronic wounds to acute ones [84].

6. Amputation

Even after major attempts to save the foot, amputation may be the only alternative. Although the extent of DFUs may allow for various types of amputation, caution should be exercised because limb amputation might increase the patient's physical, financial, and psychological burden [85–86]. The most significant aspect to consider when determining the degree of amputation is the inverse relationship between the surviving limb's length and the energy expended following amputation. In other words, the more energy expended during an action, the closer the amputation is to the body. Therefore, when feasible, distal limb-conserving amputations are recommended. Patients should also be reminded that, through advances in orthotics, prostheses, and rehabilitation, excellent outcomes are still attainable after amputation [87–88].

7. Off-Loading

Off-loading techniques, also known as pressure modulation, are considered the most significant component in managing diabetic neuropathic ulcers. Plantar shear stress and vertical plantar pressure are known causal elements of DFUs, which are caused by mechanical loads on the feet during activities and can be exacerbated by foot deformities. As a result, correcting deformities and unloading the foot are critical to preventing and managing DFUs [88–90]. Off-loading may minimize or redistribute plantar pressure zones in DFUs and protect pressure sites on the foot. Off-loading can be achieved with a variety of pressure-relieving devices, including rigid-soled postoperative shoes, supportive dressings, orthoses, total contact casts (TCC), felt padding, and foam (either removable or immovable) [91]. These procedures are chosen based on the patient's physical attributes and ability to comply with treatment, as well as the location and severity of the ulcer. Total contact casts are the most effective off-loading approach for treating neuropathic DFU. TCC is minimally padded and specifically designed to the shape of the foot, including a heel for walking [79,92–93]. They have been shown to minimize peak pressure in the forefoot by up to 87% by distributing plantar pressure across the entire weight-bearing area of the foot [94]. If a non-removable knee-high device is not tolerated, such as due to significant PAD or infection, a removable knee-high or ankle-high off-loading device may be considered, with a strong justification for the benefits of wearing the device regularly. Felted foam can be used instead of other biomechanical relief footwear [95]. If nonsurgical off-loading procedures fail to achieve adequate recovery, the IWGDF recommendations include surgical options such as Achilles tendon lengthening, metatarsal head excision, joint arthroplasty, or metatarsal osteotomy.

8. Infection treatment

Antibiotic therapy for infected DFU will initially be empirical, based on the most likely causative organism and the severity of the infection. Definitive treatment is modified based on microbiological culture results and the response to empirical therapy. According to the Infectious Diseases Society of America, infections are divided into three categories: mild infections (erythema < 2 cm), moderate infections (erythema > 2 cm), and severe infections (systemic involvement) [96]. The duration of

treatment is determined by the degree of the illness; for example, a moderate infection may require 1–2 weeks of therapy, and a severe infection 2–4 weeks or longer if osteomyelitis is present [97]. Oral antibiotics such as cephalexin, amoxicillin–clavulanic acid, and moxifloxacin can be used to treat mild to moderate infections. Severe infections are often polymicrobial, involving *Staphylococcus*, *Streptococcus*, *Enterobacteriaceae*, *Pseudomonas*, *Enterococcus*, and anaerobic bacteria such as *Bacteroides*, *Peptococci*, and *Peptostreptococci*. Severe infections should be hospitalized and treated with antibiotics effective against both gram-positive organisms as well as aerobic and anaerobic bacteria. For severe infections, intravenous antibiotics such as imipenem–cilastatin, β-lactam/β-lactamase inhibitors (ampicillin–sulbactam and piperacillin–tazobactam), and broad-spectrum cephalosporins are recommended [96,98–100].

9. Larval Therapy Or Moggot Therapy

Larval therapy was first used in the United States in 1940, but as antibiotics became available, it was abandoned. The UK reintroduced the therapy in the 1990s when bacterial resistance became more common. Despite initial resistance, maggot therapy was developed to promote wound cleaning, debridement, and healing while preserving healthy tissue. It is still a relatively new method, but it appears to be a promising approach for treating difficult-to-heal wounds. The common green bottle fly, *Lucilia cuprina*, produces medical-grade blowfly larvae, which are the most extensively used maggots for DFU treatment. The efficacy of debridement is assessed by applying maggots directly to necrotic, chronic lesions that have been cleansed and disinfected. To investigate this mechanism, diabetic individuals and different animal models of diabetic foot ulcer have been used. Following multiple rounds of maggot therapy, the wound healed and became completely free of bacteria, as evidenced by the formation of new tissue sealing the wound [54,101–102].

10. Laser therapy

Low-level laser therapy (LLLT) utilizes a low-level light source, such as light-emitting diodes. When certain criteria such as power input, dosage, time, and intervals between sessions are properly followed, this treatment is thought to be an effective therapeutic approach for wound healing. Aside from changes in cell motility, function, and signaling, LLLT may also alter metabolic and molecular pathways. These alterations speed up the healing process by boosting angiogenesis and the production of extracellular matrix components, thereby shortening the inflammatory period. While LLLT is a treatment alternative that is simple to administer, prior research indicates that it is an emerging high-cost, low-effectiveness therapy technique [54,103–104].

11. Hyperbaric Oxygen Therapy (HBOT)

Patients undergoing hyperbaric oxygen treatment consume 100% oxygen at pressures greater than 1 atmosphere. This has been found to increase tissue hypoxia, improve local tissue oxygenation, and reduce wound infection by acting as an antibacterial [105]. Despite its long history, the efficacy of HBOT as a treatment for DFUs remains disputed. While some systematic reviews found no substantial benefit of HBOT for non-ischaemic DFUs, others found that HBOT promotes healing, reduces the size of DFUs, and lowers the amputation rate [106]. HBOT may assist in promoting ulcer healing and reducing the rate of amputation in patients with ischemic DFUs, but it should not be used consistently for all DFUs. When the standard of care is inadequate, the IWGDF recommends adopting HBOT as an adjunctive treatment for neuroischemic or ischemic DFUs [107].

12. Negative Pressure Wound Therapy (NPWT)

Negative pressure wound therapy (NPWT) is a non-invasive wound closure technique that uses controlled, localized negative pressure to treat both acute and chronic wounds. This method employs sterile, latex-free polyurethane or polyvinyl alcohol dressings that are fitted to the precise size needed for each wound at the bedside

and sealed with an adhesive drape. Negative pressure in the 80–125 mmHg range is most commonly used either continuously or in cycles. The fluid extracted from the wound is collected in a container within the control unit using a vacuum mechanism [108–109]. NPWT appears to improve wound oxygenation, decrease chronic exudate and edema, reduce bacterial colonization, stimulate the creation of new blood vessels, and increase cellular proliferation. Numerous RCTs have recommended this approach as a safe and efficient supplementary treatment for DFU [108,110]. According to a recent systematic review of 11 RCTs comparing NPWT with routine dressing changes, NPWT resulted in a higher rate of full healing, a shorter healing time, and fewer amputations. There were no noticeable differences in the probability of side effects associated with the treatment [111].

13. Growth factors

Exogenous growth factors have been utilized to heal chronic wounds at a variety of distinct stages. Several growth factors can become engaged at various stages of the healing process, causing a variety of cellular and molecular reactions [112]. They can stimulate angiogenesis, alter the inflammatory response, create granulation tissue, remodel, and re-epithelialize. Several of these have also been studied in clinical trials, particularly for the treatment of diabetic foot ulcers. These include platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factors (IGF-1, IGF-2), epidermal growth factor (EGF), and transforming growth factor-β (TGF-β) [113]. Only recombinant human PDGF (rhPDGF) (Becaplermin or Regranex), a hydrogel containing 0.01% PDGF-BB (rhPDGF-BB), has proven to have higher healing rates than controls in several clinical trials and has demonstrated sufficient DFU repair efficacy to receive FDA approval. There is some dispute about this medicine's safety, and patients with neoplastic illnesses should exercise extreme caution. Innovative drug-delivery methods have been created as a result of poor growth factor formulation, such as PDGF or EGF, which may be one of the primary reasons for their limited effectiveness. Nowadays, polymeric micro- and nanospheres, lipid nanoparticles, hydrogels, scaffolds, and nanofibrous structures, which might increase the stability of the protein at the wound site and permit therapeutic modification, are being used to provide controlled growth-factor release [114]. A more current technique proposes employing biodegradable polymers containing growth factors or, as an alternative, gene-mediated therapeutic delivery to create high concentrations of the growth factor in the wounded region in a controlled manner [115]. According to certain studies, endogenous PDGF is overexpressed during the entire maturation period of human astrocytoma and promotes fibroblasts to enter tumors in melanoma cells. As a result, topical use of recombinant PDGF has the potential to promote cancer formation [116].

14. Stem cells

The idea of using stem-cell therapy to address poor wound healing is fascinating. In actuality, transplanted stem cells can release growth factors and cytokines into the damaged region, promoting angiogenesis, cell recruitment, extracellular matrix remodeling, and immunomodulatory effects [117]. Adult mesenchymal stem cells (MSC) are used in commercially available topical treatments since they have shown effectiveness in several clinical trials. Induced pluripotent stem cells (iPSCs) have emerged as a new cellular therapy in recent years, and one of their benefits is that they may be utilized as an autologous transplant with a low immunological rejection rate. Several preclinical studies on wound healing in animal models have yielded substantial data that support the potential of iPSCs being developed into a unique therapeutic tool for wound healing in humans in the near future [118–119].

15. Herbal and traditional treatment

Ayurvedic/herbal treatments are a widely used option for managing diabetic foot ulcers. Such ulcers are known as *Dushta Vrana* in Ayurveda, and treatments include oral

medicine, hemorrhaging, wound debridement, and others [120]. Acharya Sushruta, India's founder of surgery, specifies 60 procedures for addressing *Vrana* (wounds), each with its own treatment strategy [121]. In the Siddha medical system, diabetic ulcers are linked to *Madumegapun*, also known as "Valicilaippun." The Siddha basic theory classifies wounds into 16 types, which are further split into three categories: *Vali Viranam*, *Azhal Viranam*, and *Iya Viranam*. Oil-based (Thailam) medications are used to treat wounds in the Vali and Azhal categories, whereas powder-based (Chooranam/Parpam) or oil-based (Thailam) therapies are used to treat wounds in the Iya category. Because the Siddha system provides 32 various types of external therapeutic treatments, wound-care management is addressed differently. The Siddha system specifies a variety of external therapies for ulcers, including Kuttu (Bandage), Poochu (Liquid application), Podi (Powder), Kaaram (Chemical cautery), and Seelai (Medicated gauze), among others. This theory proposes that drugs are intended to negate the *Iyam* [122].

The search for new antibiotic drugs from natural plants remains appealing, as they offer alternative and safe approaches to treating diabetes. Phytochemicals discovered in traditional medicinal plants are opening doors for the development of innovative drug therapies. Studies have shown that medicinal-plant extracts can activate β-cells and restore normal granulation, indicating an insulinogenic effect in diabetic patients or animals [123]. Some of the herbal plants used for treatment of DFU are *Azadirachta indica* [124], *Diospyros melanoxylon* [123], *Terminalia arjuna*, *Commiphora mukul* [125], *Curcuma longa*, etc., due to their antidiabetic and antioxidant activity [127–128].

Discussion and Conclusion

The author has reviewed many published articles to complete this review manuscript. We have covered various treatment options for DFU. Among these, the agents used to reduce blood glucose levels hold an important role; these include insulin, metformin, thiazolidinediones, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Antimicrobial agents are also used to make the wound free from bacteria. Apart from the above therapies, advanced therapies such as hydrocolloids, hydrogels, foams, alginates, iodine preparations and silver-impregnated dressings, HBOT, VEG, VGF, and NPWT were also thoroughly discussed and included. The review also incorporates herbal and traditional treatments for DFU.

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Conflict of Interest statement

The author declares no conflict of interest.

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العلاج الدوائي المتقدم لقرحة القدم السكرية: نظرة عامة

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ملخص

تُعدّ قرحة القدم السكرية من المضاعفات الرئيسية والخطيرة لمرض السكري .وتتنوع أسباب قرحة القدم السكرية، وتشمل أسبابًا أيضية، ووعائية، وعصبية، ومناعية .ويمكن أن تحدث قرحة القدم السكرية نتيجة جفاف، أو خشونة، أو التهاب، أو تلوث ميكروبي، أو تلف أنسجة القدم، وما إلى ذلك .وتناقش هذه المراجعة بعض العوامل المهمة المسؤولة عن تطور الجروح السكرية .وتُعدّ قرحة القدم السكرية من المضاعفات الشائعة لمرض السكري، حيث تتراوح نسبة حدوثها سنويًا بين 9.1 و 26.1 مليون حالة حول العالم .وبالإضافة إلى أدوية مثل الأنسولين، والميتفورمين، والثيازوليدينديونات، والسلفونيل يوريا، ومثبطات DPP-4التي تخفض مستويات السكر في الدم، فقد أثبتت هذه الأدوية أيضًا فعاليتها في علاج الجروح المزمنة بفضل خصائصها المضادة للالتهابات .غالبًا ما تُوصف المضادات الحيوية الفموية، مثل الكليندامايسين، والأموكسيسيلين-كلافولانيك، والموكسيفلوكساسين، والسيفاليكسين، لعلاج العدوى الميكروبية .ولتسريع التئام الجروح، تُستخدم مواد مساعدة متنوعة للتضميد، مثل الهيدروكولويد، والهيدروجيل، والرغوة، والألجينات، ومستحضر اليود، والضمادات المشبعة بالفضة . تشمل العلاجات الناشئة العلاج باليرقات، والعلاج بالأكسجين عالي الضغط(HBOT) ، وعلاج الجروح بالضغط السلبي (NPWT)، وعامل نمو الخلايا الليفية(FGF) ، وعامل نمو بطانة الأوعية الدموية(VEGF) ، وعوامل النمو الشبيهة بالأنسولين(IGF1، IGF2) ، وعامل نمو البشرة(EGF) ، والعلاج بالخلايا الجذعية .تُستخدم هذه العلاجات لمعالجة ضعف التئام الجروح لدى مرضى السكري.

الكلمات الدالة: قرح القدم السكرية، العلاج الدوائي، المضادات الحيوية، عوامل النمو، الهلاميات المائية، العلاج بالخلايا الجذعية

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