https://doi.org/10.48047/AFJBS.6.14.2024.11314-11341

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Exploring Nerve Complications Leading to Foot Lesions: The Journey from Diabetic Neuropathy to Post-COVID-19 Complications- A Review

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Volume 6, Issue 14, Aug 2024

Received: 15 June 2024

Accepted: 25 July 2024

Published: 15 Aug 2024

doi: 10.48047/AFJBS.6.14.2024.11314-11341

Abstract

Diabetic neuropathy, a common complication of diabetes mellitus, manifests as progressive nerve damage affecting various organ systems, notably leading to diabetic foot ulcers (DFUs). This review synthesizes current knowledge on the pathophysiology, risk factors, and classifications of DFUs. It highlights the significant impact of hyperglycemia, hypertension, dyslipidemia, age, glycemic variability, and genetic factors on neuropathy development in diabetes patients. Various classification systems, including Wagner, PEDIS, University of Texas, and S(AD)SAD, are discussed for their utility in assessing DFU severity and guiding treatment decisions. The COVID-19 pandemic worsened DFU management globally, increasing amputation rates in many countries. The management strategies like glycemic control, drug therapy, vascularization enhancement, exercise, and nutritional interventions. Advanced therapies such as hyperbaric oxygen therapy, electrical stimulation, negative pressure wound therapy, and bioengineered skin show promise in treating severe DFUs. This comprehensive review underscores the multidimensional approach required for effective DFU management, aiming to mitigate complications, reduce amputations, and improve patient outcomes amidst evolving clinical landscapes.

Keywords- Diabetes, Diabetic foot ulcer (DFU), diabetic peripheral neuropathy, pathogenesis, COVID-19, Glycemic Management

Abbreviation- (DFU) Diabetic Foot Ulcer, (DN) Diabetic Neuropathy. (DPN) Diabetic Peripheral Neuropathy, (BMI), Body Mass Index, (CKD) Chronic Kidney Disease, (ET) Exercise Therapy, (PP) Plantar Pressure, (25OHD) 25-Hydroxyvitamin D, (IU) International Unit, (PCTA) Percutaneous Transluminal Angioplasty, (HBOT) Hyperbaric Oxygen Therapy, (ES) Electrical Stimulation, (NPWT) Negative Pressure Wound Treatment, (BES) Bio-Engineered Skin, (ECM) Extracellular Matrix, (PAD) Peripheral Arterial Disease, (CLI) Critical Limb Ischemia, (SIRS) Systemic Inflammatory Response Signs.

Introduction

Diabetes, a chronic condition marked by dysregulated blood sugar levels, can give rise to an array of debilitating complications, and one that stands out in particular for its widespread prevalence and debilitating impact is diabetic neuropathy.

Krause and De Vito (2023) pointed out that Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that affects approximately 1% of the population. It is triggered by genetic and environmental factors, destroying pancreatic beta cells and resulting in insulin deficiency. On the other hand, type 2 diabetes mellitus (T2DM) is primarily characterized by insulin resistance and a gradual decline in insulin production from pancreatic beta cells. While T1DM is an autoimmune condition, T2DM develops mainly due to metabolic factors and impaired insulin response.

Tinajero and Malik (2021) reported that the occurrence of type 2 diabetes (T2D), on a scale, has notably increased in the last thirty years. The standardized rates stood at 6.0% for men. 5.0% for women in 2019 up from 3.9% and 3.5% in 1990 respectively. Currently, it is most prevalent among individuals aged between 55 to 59 showing an onset in men. This trend suggests a rise in age groups due, to the escalating levels of obesity.
In 2019, Pradeepa and Mohan (2021) reported that 77 million individuals, in India were reported to have diabetes with projections indicating that this figure will surpass 134 million by the year 2045.

(Pop-Busui *et al*., 2017) explained that diabetic neuropathy is a type of nerve damage that occurs as a long-term complication of diabetes mellitus, characterized by progressive loss of nerve fiber function. It affects multiple organ systems and can manifest in various forms, including peripheral, autonomic, proximal, and focal neuropathies. The sensory symptoms are varied and usually start in the feet and move proximally.

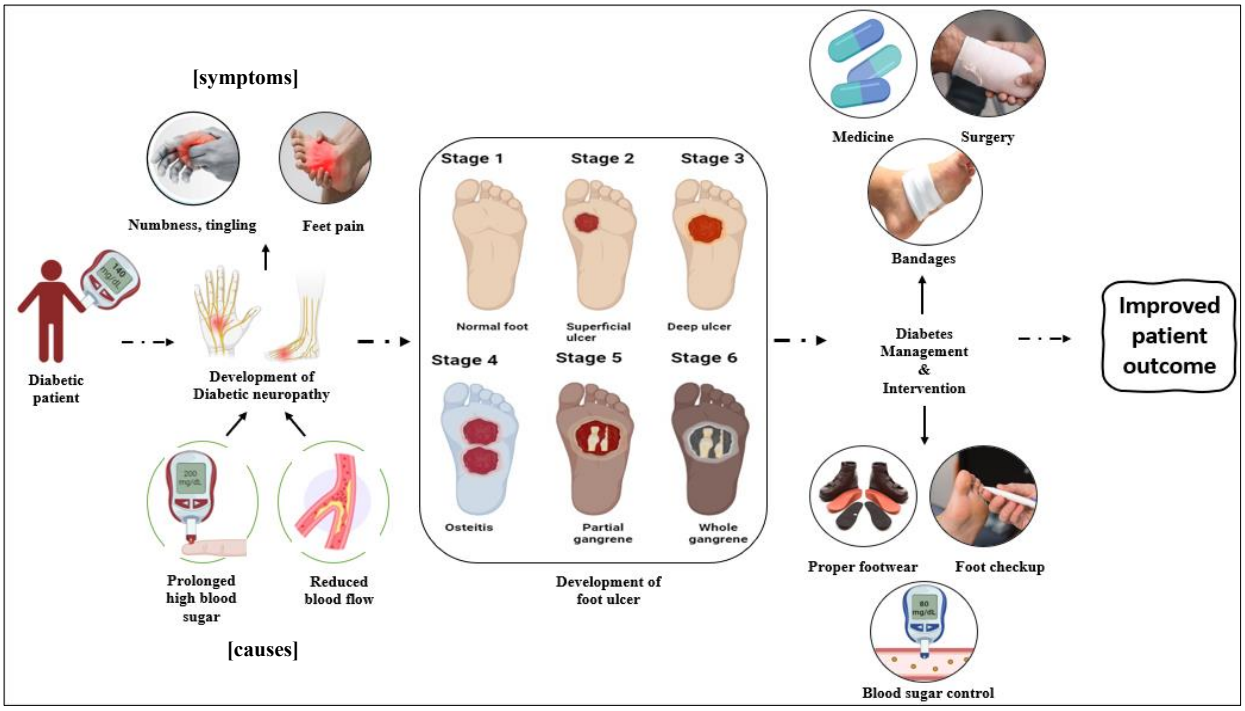

Figure1. When a diabetic patient has persistently high blood sugar, it reduces blood flow and causes diabetic neuropathy, which causes tingling, numbness, and pain in the feet. Ulcers may form on the foot as the condition worsens; these can occur in six stages: normal foot, osteitis, superficial ulcer, deep ulcer, partial gangrene, and complete gangrene. At every stage, adequate diabetes management and intervention—including blood sugar control, frequent foot exams, appropriate footwear, bandages, medicines, and surgery when needed—are essential. The ultimate goal of these therapies is to enhance patient outcomes by preventing serious complications and fostering recovery.

(Neville RF *et al*.,2016) mentioned that diabetic foot ulcers frequently occur as a complication of diabetes mellitus that is not well controlled, due, to foot maintenance, peripheral vascular issues, underlying nerve damage, or inadequate blood sugar regulation. It is also a prevalent cause of lower limb amputations and osteomyelitis of the foot.

More recently, statistics from the UK in 2019 indicate that, conservatively, the yearly cost of diabetic foot issues surpasses the UK £900 million, or almost 1% of the National Health Service's overall budget, as pointed out by (Kerr M *et al*.,2019)

Crawford F *et al*.,2020) reported in his studies that In India, 4.54% of individuals with type 2 diabetes mellitus who were recently diagnosed also had diabetic foot ulcers; of them, 46.1%

had neuropathic, 19.7% had ischemic, and 34.2% had neuroischemic foot ulcers.

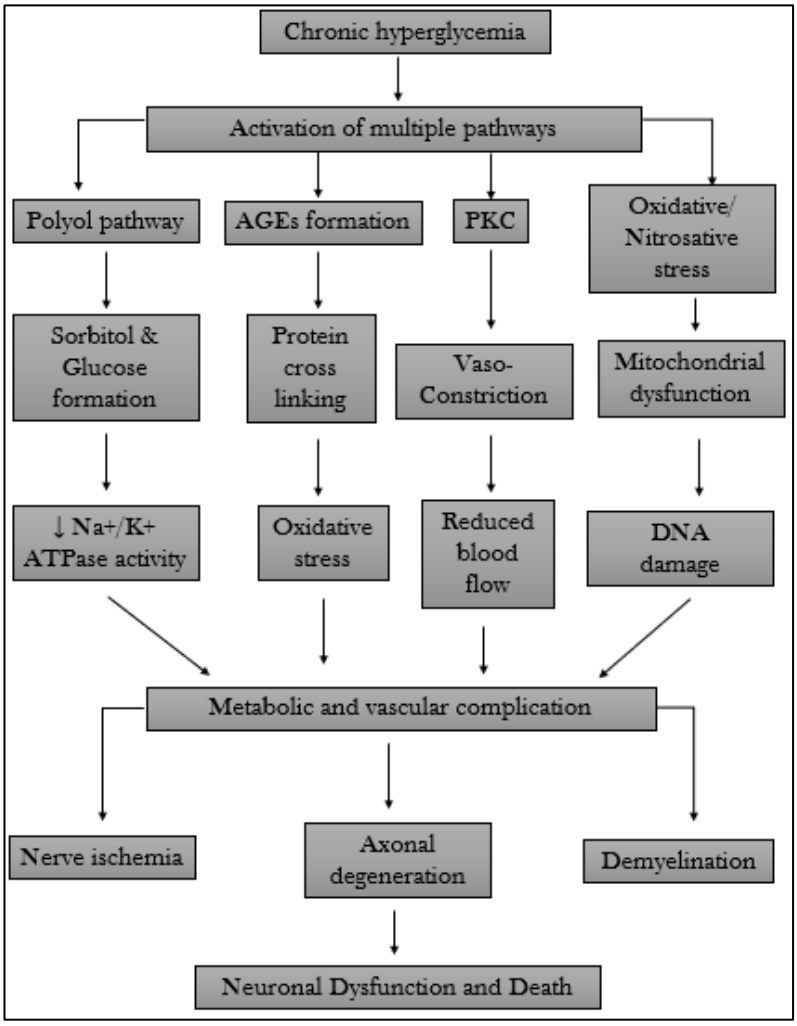

Figure 2. How Chronic Hyperglycemia Inflicts Nerve Damage (AGEs-Advanced glycation end products, PKC-Protein kinase C)

2.1 Risk factors

The development of neuropathy, a complication of diabetes, is influenced by different factors that determine the progression and severity of this condition.

2.1.1 Hyperglycemia

(Yagihashi S *et al*.,2011) explained that elevated glycated haemoglobin levels are strongly linked to an increased occurrence of neuropathy.

Papanas and Ziegler (2015) stated that hyperglycemia is a major risk factor for diabetic sensorimotor polyneuropathy (DSPN) in both type 1 (T1D) and type 2 diabetes (T2D). Studies show that each 1% increase in HbA1c is associated with a 10-15% higher frequency of DSPN. Thus, the effectiveness of strict glycemic control in reducing DSPN incidence and progression has been widely studied. A significant difference has been found between T1D and T2D: a meta-analysis indicated that optimized glycemic control significantly prevents clinical DSPN and reduces neurological deficits in T1D, but this effect is not significant in T2D.

A meta-analysis reported by (Ang L *et al*.,2014) revealed that optimal blood glucose control decreases the incidence of DN in types 1 and 2 DM individuals.

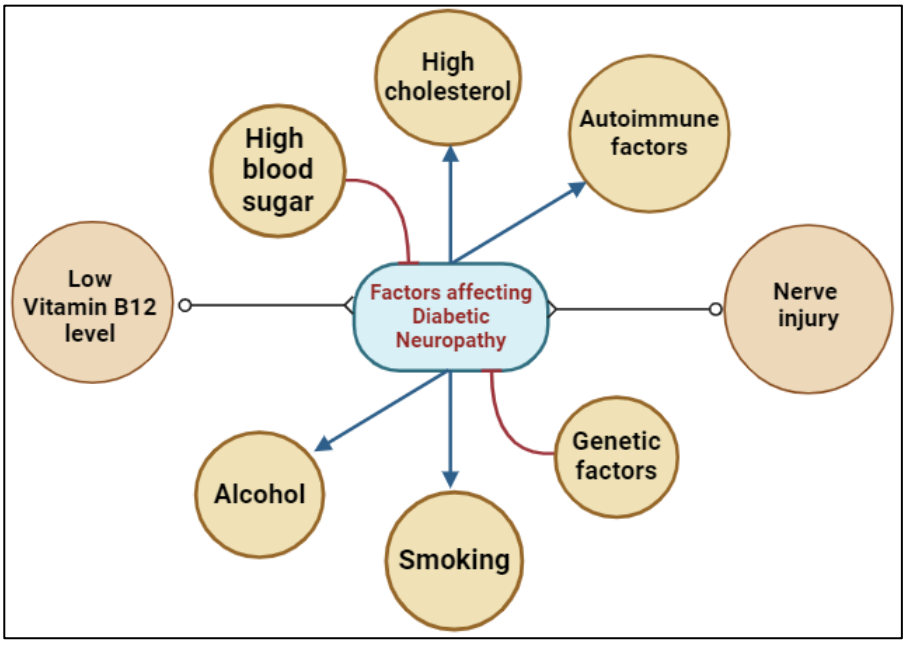

Figure 3. Factors affecting diabetic neuropathy

2.1.2 Blood pressure

(Gregory JA *et al*., 2011) analyzed that in individuals with diabetes, hypertension can both contribute to peripheral neuropathy and act as a separate risk factor for neuropathy.

(Huang L *et al*.,2020) mentioned that increased blood pressure exacerbates diabetic neuropathy (DN) by causing vascular injury, endothelial dysfunction, and insulin resistance, which lead to a cycle of inflammatory damage, reduced arterial compliance, and heightened cardiovascular risk, further complicating DN management.

2.1.3 Triglycerides

(Wiggin TD et al.,2009) reported in their studies that in patients with worsening diabetic neuropathy, there's a notable link between high triglyceride levels and reduced peroneal motor nerve conduction velocity (NCV) at the initial assessment. Elevated triglyceride levels are associated with the progression of diabetic neuropathy. The study indicates that dyslipidemia, particularly high triglycerides, contributes to nerve damage in individuals with diabetes. This suggests that managing lipid levels could be crucial in preventing or slowing down neuropathy progression.

2.1.4 Age

(Tesfaye *et a*l.,2010) stated that diabetic neuropathy risk increases with age, affecting elderly individuals more frequently and severely than younger patients. This age-related vulnerability is due to natural changes in nerve function and metabolism over time. As a result, older diabetic patients need more vigilant monitoring and tailored management of their neuropathic symptoms to prevent complications. This highlights the importance of age-specific care approaches in diabetes management, particularly for neurological complications.

2.1.5 Glycemic variability

(Zhang X *et al*.,2021) reported that increased glucose variability (GV) is a significant risk factor for diabetic neuropathy (DN), impacting both type 1 and type 2 diabetes. Studies indicate that GV contributes to oxidative stress, inflammation, and axonal degeneration, all of which are critical factors in the development of DN. Markers of GV, such as the mean amplitude of glycemic excursions (MAGE) and the standard deviation of blood glucose levels, are correlated with neuropathic pain, motor and sensory axonal dysfunction, and a heightened risk of painful DN. Additionally, the onset of DN is closely linked to oxidative stress and inflammatory reactions triggered by GV, particularly through the NF-kB pathway.

2.1.6 Genetic factors

(Tordai DZ *et al*., 2024) highlighted in his studies that neuropathy in Type 2 Diabetes is influenced by genetic factors, which play a crucial role in its development. The interplay between genetic factors and environmental influences is essential for the onset of neuropathy. Specific genetic

variants, like rs2032930 and rs2032931 of the RMI2 gene, and rs604349 of the MYBPHL gene, increase the risk of neuropathy development.

3. Foot lesions in Diabetic neuropathy

Diabetic foot ulcers (DFU) are a significant contributor to hospitalization, morbidity, and mortality, affecting around 6.3% of diabetes patients globally.

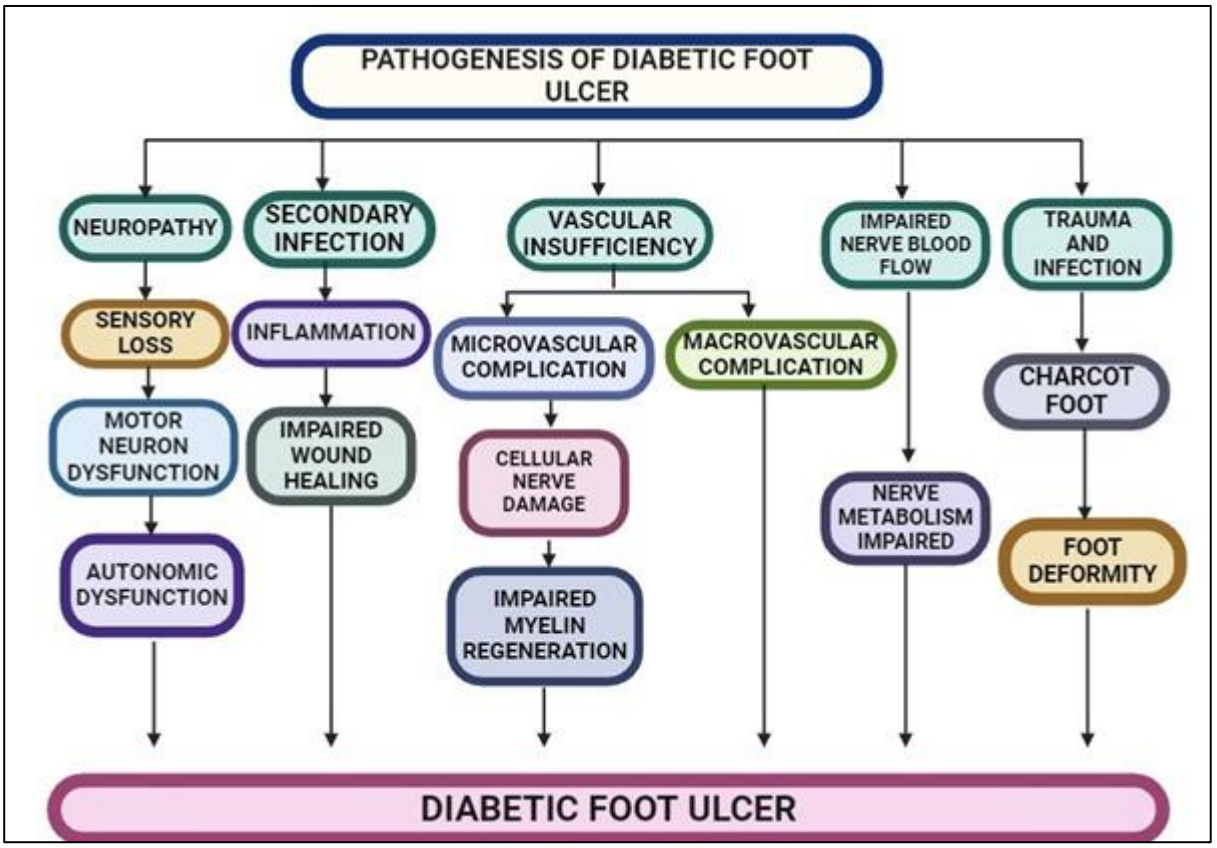

Figure 4. Pathogenesis of diabetic foot ulcer, outlining the various contributing factors and their interrelations

A study conducted by (Abuhay *et al.*, 2022) of 539 diabetes patients found 65 (12.1%) developed foot ulcers. Diabetic neuropathy increased risk by 2.61 times. Other risk factors included rural residence, arterial disease, and blood sugar fluctuations. The incidence rate was 2.26 per 1000 person-months.

(Wang X *et a*l., 2022) pointed out that in the early stages of diabetic neuropathy (DN), patients often experience pain and tingling. As the condition progresses, symptoms evolve into numbness

and weakness. Patients report a combination of pain and dullness, decreased motor function, and limb sensation, which can lead to imbalance and falls. Diabetic foot ulcers (DFU) significantly increase the risk of non-traumatic amputations and mortality. The development and healing of DFU are influenced by complex factors such as peripheral artery disease (PAD) and neuropathy, whose impact varies over time. Accurate diagnosis and treatment of DFU require standardized, widely recognized classification and scoring criteria to ensure effective management and improved outcomes.

3.1 Classification system

3.1.1 Megitt-Wagner

This classification system has been historically the most widely used, though its usage has declined in recent years. It was first described by Meggitt in 1976 and later popularized by Wagner in 1979.

Wagner (1981) reported this classification system which assesses diabetic foot ulcers based on the depth of the ulcer and the extent of tissue involvement. It categorizes ulcers into six grades, ranging from Grade 0 (no open lesions) to Grade 5 (extensive gangrene involving the entire foot). This system helps clinicians determine the severity of the ulcer, guide treatment decisions, and predict outcomes.

Grade	**Wagner Ulcer Classification system.**
Grade 0	No ulcer in a high-risk foot
Grade 1	Superficial ulcer involving skin not underlying tissues
Grade 2	The ulcer penetrates the tendon, bone, or joint capsule, usually accompanied by some level of bony prominence.
Grade 3	Deeper tissues are involved with abscesses, osteomyelitis, or tendinitis, usually extending along midfoot tendon sheaths.
Grade 4	Gangrene affects part of the toe, toes, or forefoot, often requiring surgical removal.
Grade 5	Gangrene involves the entire foot or a significant part, necessitating below-knee amputation.

Table 1 Wagner classification system

3.1.2 PEDIS classification system

(Noorsyawala *et a*l., 2020) reported that the PEDIS classification system was developed by the International Working Group of the Diabetic Foot (IWGDF) to unbiasedly evaluate and disseminate information regarding DFU. This system categorizes DFU into five areas: perfusion, extent, depth, infection, and sensation.

The PEDIS classification system was mainly developed for research purposes mentioned by (Chuan F *et al*.,2015)

Grade	Perfusion	Extent	Depth	Infection	Sensation	Score
1	No PAD	Skin intact	Skin intact	None	No loss	0
2	PAD, No CLI	<1cm^2	Superficial	Surface	Loss	1
3	CLI	1-3 cm^2	Fascia, muscle, tendon	Abscess, fasciitis, septic arthritis		2
4		>3 cm^2	Bone or joint	SIRS		3

Table 2. PEDIS classification system

3.1.3 The University of Texas classification system

(Vera-Cruz *et a*l.,2020) stated that The University of Texas classification system for diabetic foot conditions is regarded as superior to the Wagner system in predicting major amputations. It employs a matrix format, with grades on one axis and stages on the other, to evaluate the severity of diabetic foot issues. This approach allows for a more comprehensive assessment of the condition.

(Armstrong D *et al*.,1998) mentioned the classification system of Texas along with the grades.

Stage	**Grade 0**	**Grade I**	**Grade II**	**Grade III**
A	Pre- or post-ulcerative lesion	Superficial ulcer, not involving tendon capsule or bone	Ulcer penetrating to tendon or capsule	Ulcer penetrating to bone or joint
B	Infection	Infection	Infection	Infection

C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection & ischemia	Infection & ischemia	Infection & ischemia	Infection & ischemia

Table 3. University of Texas classification system

3.1.4 The S(AD)SAD classification system

Macfarlane and Jeffcoate (1999) stated the S(AD) SAD system is a comprehensive classification method for diabetic foot ulcers that evaluates five critical factors: Size (considering both area and depth), Sepsis (assessing infection), Arteriopathy (evaluating blood flow issues), and Denervation (addressing nerve damage or neuropathy). This system stands out by explicitly including neuropathy, a crucial factor in diabetic foot ulcers that is not mentioned in other classification systems, such as the San Antonio method.

Grade	Area	Depth	Sepsis	Arteriopathy	Denervation
0	Skin intact	Skin intact	No infection	Pedal pulses palpable	Pinprick sensation
1	<10 mm^2	skin and subcutaneous tissues	Surface infection.	Diminution of both pulses or absence	absent pinprick sensation
2	10-30 mm^2	Penetrating to tendon, periosteum, or joint capsule	Cellulitis	Absence of both pedal pulses	Absence of pinprick
3	>30 mm^2	Involving bone or joint spaces	Osteomyelitis	gangrene	Charcot foot

Table 4. S(AD)SAD classification system

4. "The Collision of Crises: Exploring COVID-19's Influence on Diabetic Foot Ulcers"

The COVID-19 pandemic, particularly the lockdown measures, significantly impacted patients with diabetes and diabetic foot ulcers (DFUs).

(Caruso P *et al*.,2020) analyzed that the management of patients with diabetic foot ulcers (DFUs) was severely disrupted by the COVID-19 pandemic lockdown. As a result, there were three times as many occurrences of severe DFU, greater hospitalization rates, and an increased risk of amputations. Compared to patients admitted in 2019, those admitted during the lockdown were more frequently in emergencies and had a far higher rate of gangrene. This demonstrates the negative effects of care disruptions on DFU management and patient outcomes.

Viswanathan and Nachimuthu (2023) stated that due to the COVID-19 pandemic, China had a notable decrease in hospitalizations for diabetic foot issues and an increase in severe amputations over the first three months and the entirety of 2020.

(Yunir E et al., 2022) Reported that during the pandemic, there was a 54.1% increase in major amputations in South India compared to the pre-pandemic period.

(Ahmed J et al., 2022) mentioned that In Indonesia, during the pandemic, the percentage of amputations increased to 39.3% from 56.3%, while significant amputations increased to nearly twice the pre-pandemic level (20.2% from 39.4%).

Chadwick P (2023) conducted research in Bangladesh and found that during the pandemic, there was a higher rate of major and minor amputations in addition to complete amputations.

5. Diagnosis of diabetes foot ulcer

5.1 Physical assessment

The comprehensive physical examination of the diabetic foot integrates assessments across dermatological, vascular, neurological, and musculoskeletal systems.

(Fard AS *et al.,* 2007) mentioned in his studies that, dermatologically, the physician meticulously inspects the skin on the legs and feet, examining all surfaces including dorsal, plantar, medial, lateral, and posterior regions, with particular attention to each toenail. A crucial aspect involves comparing the condition of the foot skin with that of the arms and hands to detect any discrepancies. Special observations include identifying issues like peeling skin, maceration, or fissuring of the interdigital areas and noting common diabetic skin conditions such as diabetic dermopathy, necrobiosis lipoidica diabeticorum, and bullous diabeticorum.

5.2 Examination of ulcer

(Grayson ML *et al.*, 1995) reported that, a sterile stainless-steel probe is used to clinically assess an ulcer's location, size, shape, depth, base, and margins. The presence of granulation tissue or slough on the ulcer floor helps determine subsequent management. Diagnosing soft tissue infections in diabetic patients can be difficult due to the potential absence of inflammatory signs. Infections are primarily identified through clinical signs such as redness, warmth, tenderness, purulent secretions, and fever.

5.3 Neurological testing

(Koenig, 1976 and Rabjohn, 2002) pointed out that, sensory neuropathy in diabetic foot ulcers is assessed using monofilaments and a biothesiometer, with Semmes-Weinstein monofilaments recommended for predicting ulceration and amputation risk. Annual nylon monofilament testing is suggested for all diabetic patients to detect peripheral neuropathy early. Additionally, vibratory sensation testing with a 128 Hz tuning fork on the great toe helps assess metabolic neuropathies, and evaluating pain sensation is also essential.

5.4 Imaging

(Rajbhandari, 2002 and Madan, 2013) reported that X-rays are valuable for assessing foot ulcer depth, detecting bone infections, and identifying neuroarthropathy, revealing issues like bony erosions and fractures. Magnetic Resonance Imaging (MRI) is preferred for diagnosing foot problems in diabetic patients, particularly effective in detecting infections and Charcot neuroarthropathy (CN). MRI also assesses infection extent by visualizing ulcer depth, edema, and fluid collections in soft tissues, joints, and tendon sheaths. Positron emission tomography (PET) is highly specific for detecting osteomyelitis.

6. "Healing Steps: Best Practices in Diabetic Foot Ulcer Management"

6.1 Glycemic control

(Callaghan BC *et al.,* 2012) reported that research shows individuals with insulin-dependent diabetes mellitus, strict glycemic management postpones the development of diabetic retinopathy, nephropathy, and neuropathy and slows its progression. (Tesfaye S *et al*., 2013) reported that a meta-analysis examining the impact of strict glycemic management on diabetic neuropathy found

that improved glycemic control, particularly in Type 1 diabetes mellitus, considerably lowers the chance of acquiring clinical neuropathy.

6.2 Drug therapy

(Tiktin M *et al*., 2016) mentioned that, for pain management, the National Institute of Clinical Excellence advises using pregabalin and duloxetine as first-line medications [38]. (Lim JZ *et al*., 2017) reported that, in a case-controlled study, diabetes awareness and self-management practices increased prescription adherence to oral diabetic drugs. Dixon and Edmonds (2021) suggested that, hydrogel dressings speed up the process of autolytic debridement-induced wound healing. Autolytic debridement is a process that partly digests and rehydrates devitalized tissue by using the body's enzymes and moisture.

6.3 Improving vascularisation

(Hsu CR *et* al., 2015) reported that increased perfusion following revascularization of severely ischemic legs is linked to a further decline in the risk of amputations.

Zhang and Lv (2016) mentioned that local insulin injections have been demonstrated to notably enhance vascularization in diabetic foot ulcers. Enhanced angiogenesis, evidenced by the appearance of new vessels as early as 3 days post-injection, is observed in the insulin-treated group. Moreover, microvessel density (MVD) shows a significant increase starting from day 5 after treatment, highlighting improved vascularization compared to untreated control groups.

6.4 Exercise therapy

(Sacco IC *et al*., 2009) mentioned in his study, exercise therapy (ET) may have a significant therapeutic impact on preserving and enhancing the biomechanics of the foot and reestablishing a physiological pattern. If these findings hold, peak plantar pressure (PP) during routine activities may decline. (Richardson JK *et al.,* 2001) reported that, elderly individuals with mild to severe DPN, three weeks of regular exercise designed to develop immediately available ankle strength improves balance.

(Zhang X *et al.,* 2014) pointed out that, certain walking patterns, including shuffling, hip pull-off, step-to walking, and backward walking, have been shown to help lower forefoot peak plantar pressures in DPN patients. (Allet L et al., 2010) reported in his studies that, after 12 weeks of

training, older type 2 diabetes patients' balance, gait speed, and fear of falling improve. According to Kwon and Mueller (2001), these modified gait patterns could further harm posture, the musculoskeletal system, and biomechanics affecting the spine, hip, knee, or ankle joint.

6.5 Diet

(Da Porto A *et al.,* 2022) pointed out that, nutritional therapies can accelerate the recovery from DFU. When progress toward DFU closure is not accomplished, current Australian guidelines advise evaluating nutritional status and using oral supplements (ONS) when an oral diet is insufficient to meet nutritional needs.

6.5.1 Proteins and amino acids

(Eneroth M *et al.,* 2004) mentioned that the evidence of these compounds' beneficial effects on wound healing, proteins, and amino acids are the most often utilized nutritional supplements to promote the healing of diabetic foot wounds.

(Wong A *et al*., 2018) reported that an RCT with 270 patients examined the effects of supplementing with arginine, glutamine, and b-hydroxy-methyl butyrate can be used to heal diabetic foot ulcers. The present research findings did not clearly show how proteins and amino acids affected the healing of diabetic foot wounds. However, there is some indication that they were effective in speeding up the healing process.

6.5.2 Polyunsaturated omega-3 fatty acids

(Ohue-Kitano R *et al*., 2018) suggested that it has long been believed that long-chain omega-3 polyunsaturated fatty acids and their bioactive metabolites, such as resolvins, marine, and protection, are potent negative modulators of acute inflammation and inducers of its resolution.

6.5.3 Probiotics

(Da Porto A *et al*.2022) proposed that members of the Lactobacillus and Bifidobacterium genera, strains from other bacterial species (*Propionibacterium acidilactici, Lactococcus lactis, Leuconostoc mesenteroides, Bacillus subtilis, Streptococcus thermophilus*), and yeasts (*Saccharomyces boulardii*) are among the most often used probiotics as supplements.

6.5.4 Vitamin C

(Christie-David DJ *et al*.,2017) mentioned in their study that ascorbic acid, another name for vitamin C, is a water-soluble vitamin essential to several biological processes leading to wound healing. These processes include the production of collagen, immune system modulation, and bone and cartilage preservation. (Pena G *et al.,* 2020) reported that, individuals who are 21 years old and older, it is recommended to take a daily dosage of 75 mg for women and 90 mg for men. In a prospective trial involving 131 participants, it was found that a deficiency of ascorbic acid (vitamin C) was associated with a more severe form of diabetic foot ulcer.

(Gunton JE *et al.,* 2021) pointed out that, individuals having diabetes with lower limb sores, heal more quickly after taking vitamin C supplements. This study further explained that Vitamin C enhances collagen formation and supports immune function, aiding in foot ulcer healing. A randomized, double-blind, placebo-controlled trial found that patients receiving vitamin C had a median healing rate of 100%, compared to -14% in the control group. Many patients were vitamin C deficient, highlighting the need for supplementation. This suggests that vitamin C could be a low-cost, effective strategy to improve healing outcomes in patients with foot ulcers, especially those with low vitamin C levels.

6.5.5 Vitamin D

(Pena G *et al.,* 2020) suggested that, vitamin D, a fat-soluble vitamin, aids in the body's absorption of some calcium and phosphorus, both of which are necessary for bone formation. Patients suffering from DFU have low circulating levels of 25 (OHD). (Razzaghi R *et al.,* 2017) reported that, double-blind, placebo-controlled, randomized clinical trial after 12 weeks of intervention, vitamin D supplementation significantly reduced ulcer length, width, depth, and erythema rate compared to placebo.

6.5.6 Trace elements

Zinc, copper, chromium, selenium, and magnesium are vital trace elements. **(**Afzali H *et al.,* 2019) reported that, study conducted and after 12 weeks of treatment, patients given 250 mg of magnesium oxide showed improvements in ulcer size. They were randomized to either a placebo or 250 mg of magnesium oxide with 400 IU vitamin E daily for 12 weeks and showed that magnesium oxide and vitamin E can reduce DFU.

6.6 Surgery treatment

(Tao F *et al.,* 2020) pointed out that, in the surgical management of diabetic foot sores and neuropathic ulcers, debridement is crucial. The goal of this is to reach healthy tissue. Advanced osteitis, abscess, gangrene, and infected neuropathic ulceration are some of the symptoms.

Aderibigbe and Buyana (2018) mentioned that bandages play a crucial role in the management of diabetic foot ulcers. They serve multiple purposes, including wound protection, moisture management, and promoting healing. The choice of bandage depends on the ulcer's characteristics, location, and stage of healing.

Diabetes-related foot ulcer bandages include alginates, which are highly absorbent and good for wounds with a lot of exudates. Foam dressings, which cushion and keep the wound moist. Hydrocolloids, create a gel-like substance when in contact with exudate. Hydrogels keep the wound moist and are good for dry wounds; iodine preparations, have antimicrobial qualities. Low-adherence dressings, which minimize trauma during dressing changes. Silver-impregnated dressings offer antimicrobial protection and help lower the risk of infection.

Dressing	**Overview**	**Tips for Utilisation**
Alginates	Anti-hemorrhagic and bacteriostatic features combined with high absorbency.	Ideal for cavitating wounds.
Foam Dressing	Possesses qualities of thermal insulation and moderate absorption.	Apply on both thin and thick wounds that exude fluid.
Hydrocolloids	Absorbent, promoting autolysis and rehydration. promotes granulation.	Effective for necrotic, sloughy, dry wounds. Avoid applying anything to infected wounds.
Hydrogels	liquid-donating, absorbent, and helps in autolysis.	Productive for necrotic, sloughy, dry wounds. should be careful of concurrent or suspected infections.
Iodine Preparations	Possesses antibacterial qualities and is partially absorbent.	Discoloration of wounds and avoid in case of thyroid, an iodine allergy, or in pregnancy.

Low-Adherence	Hypoallergenic with minimal absorption.	Standard care for ulcers caused by diabetes. often combined with antimicrobial agents.
Silver-impregnated	Antiseptic and absorbent qualities.	Beneficial for DFU that are infected. Avoid in case of hypersensitivity to silver.

Table 5. A brief description of the several dressings used to treat diabetic foot ulcers

6.6.1 Debridement

(Moore E *et al.,* 2018) reported that, in addition to being infected by many microbes, severe DFUs are frequently linked to necrotizing fasciitis on the feet or legs, septic arthritis, subfascial abscesses, and deep local abscesses. These infections are the primary cause of amputation in persons with diabetes since treatments for them are usually ineffective. Septic shock and maybe death are possible outcomes of severe DFU infections in people. Because of this, debridement surgery is done on infected ulcers.

6.6.2 Amputation

(Liao X *et al*., 2022) mentioned that amputation is considered a surgical treatment for diabetic foot ulcers when the ulcers are severe and unresponsive to other treatments, especially in cases involving gangrene or significant infection. The decision to amputate takes into account various factors, including the patient's overall health, the extent of the ulcer, and the presence of vascular disease. For patients with diabetes, there is a 25% lifetime risk of developing a foot ulcer, with 14% to 24% potentially requiring a major or minor lower limb amputation due to complications such as severe gangrene

6.7 Interventional therapy

Percutaneous transluminal angioplasty (PCTA)

(Kassimis G *et al*., 2017) mentioned that Percutaneous Transluminal Coronary Angioplasty (PCTA) is crucial for diabetic patients with peripheral artery disease (PAD), as it improves blood

flow to the feet by opening narrowed arteries. This enhanced circulation is vital for healing foot ulcers, and delivering essential oxygen and nutrients to the affected areas. PCTA also reduces the risk of severe complications, such as amputation, by promoting faster woundhealing and better limb preservation. Additionally, being minimally invasive, PCTA offers quicker recovery times and less postoperative pain compared to surgical options, making it ideal for diabetic patients with other health issues.

7. Advanced therapies and emerging solutions

7.1 Hyperbaric oxygen therapy

(Huang *et al*., 2015) mentioned in their studies that adjunctive HBOT can improve the healing rates of diabetic foot ulcers compared to standard care alone. This is particularly important for patients with chronic, non-healing ulcers, as it may lead to better outcomes and reduce the risk of complications Reduction in Amputation Rates: One of the primary aims of using HBOT is to prevent major amputations in patients with severe diabetic foot ulcers. The therapy is believed to decrease the need for amputations by promoting healing and reducing the severity of the ulcers

Al-Waili and Butler (2006) reported that clinical experiences indicate that HBO2 therapy significantly enhances wound healing in diabetic ulcers. It increases wound granulation, tissue formation, and accelerates wound contraction and closure, which are critical for effective healing.

7.2 Electrical stimulation

(Peters EJ *et al*.,2001) reported that electrical stimulation shows promise in enhancing the healing of diabetic foot ulcers by improving blood flow, reducing infection, and enhancing cellular responses—addressing common deficiencies in diabetic wound healing. A randomized clinical trial found a higher healing rate in patients receiving electrical stimulation (65%) compared to sham stimulation (35%). Their Studies also indicate that electrical stimulation increases tissue perfusion, crucial for patients with impaired circulation due to diabetes. Overall, when combined with appropriate off-loading and local wound care, electrical stimulation appears to be a beneficial adjunct therapy for improving diabetic foot ulcer outcomes.

According to (Petrofsky JS *et al*.,2010), electrical stimulation (ES) is an ideal supplementary treatment for DFU recovery. And also reported that in the group that received both local heat and

electrical stimulation (ES), the average wound area decreased by 68.4% and the volume by 69.3% over one month, a notable improvement compared to the local heat-only group, which showed a 30.1% decrease. Additionally, skin blood flow, measured with a laser Doppler flow imager, increased significantly more in the ES + heat group (152.3%) compared to the heat-only group (102.3%).

7.3 Negative pressure wound therapy

Armstrong and Lavery (2005) stated that Negative pressure wound treatment (NPWT) is a non-invasive technique for closing wounds that helps cure both acute and chronic wounds by applying controlled, localized negative pressure.

(Venturi ML *et a*l.,2005) analyzed that the use of sterile, latex-free polyurethane or polyvinyl alcohol foam dressings, which are fitted to the proper size for each wound at the bedside and sealed with an adhesive drape. The most frequent negative pressure range, either continuously or in cycles, is 80–125 mmHg.

(Richmond NA *et al*.,2013) explained that applying mechanical stress seems to be the reason for NPWT's ability to get rid of edema and chronic exudate, reduce bacterial colonization, encourage the growth of new blood vessels, increase cellular proliferation, and improve wound oxygenation.

(Vikatmaa P *et al*., 2008) mentioned that in a study involving 24 patients with diabetic foot ulcers, NPWT led to a faster formation of granulation tissue compared to saline bandages, with an average of 11.3 days for NPWT versus 15.8 days for the control group and a significant reduction in the surface area of the ulcers.

7.4 Bioengineered skin

(Teng YJ *et al*., 2010) explained that Bioengineered skin (BS) is effective in treating diabetic foot ulcers (DFUs) by providing a supportive matrix that promotes healing. It supplies essential materials and stimulates growth factors and cytokines crucial for wound repair. BS treatment accelerates wound closure compared to traditional methods and reduces infection risks associated with prolonged ulcers. Meta-analyses show that BS not only enhances healing effectiveness but also improves safety by lowering infection rates. This approach addresses the complex challenges

of DFUs, which are often complicated by neuropathy and vascular issues, making BS a promising option when conventional treatments fall short.

Conclusion and perspective

In conclusion, diabetic neuropathy is a challenge in the management of diabetes mellitus, exerting a profound impact on patients' quality of life and healthcare systems worldwide. The interplay of metabolic dysregulation, vascular damage, and neuroinflammatory processes highlight how diverse this illness is. Effective management strategies constant monitoring of blood sugar levels, proper foot care, and timely intervention are crucial in mitigating the progression of diabetic neuropathy and preventing debilitating complications such as diabetic foot ulcers. Emerging therapeutic modalities, including advanced wound care technologies and targeted pharmacotherapies, offer promising avenues for improving outcomes in affected individuals. However, the COVID-19 pandemic has posed unprecedented challenges, further highlighting the need for resilient healthcare infrastructures and integrated care approaches to address diabetic foot ulcer management effectively.

Moving forward, improving early identification, intervention, and comprehensive care of diabetic neuropathy will need ongoing review efforts, multidisciplinary collaboration, and patient education. By giving comprehensive care strategies, we can strive towards alleviating the burden of this widespread complication.

Acknowledgments: We are thankful to the chairman, management, principal, teaching and non-teaching staff of Acharya & BM Reddy College of Pharmacy, Bengaluru for providing us with necessary support throughout our review submission

Author contribution- Dr. Suresh Janadri, M Pharm., Ph.D. has designed and guided the study, Ms. Shreyashi Chakraborty collection of data and materials., Dr. Manjunatha P M, M.Pharm., Ph.D. has reviewed the data. Dr. Uday Raj Sharma, M.Pharm., Ph.D., has supported finalizing the article. Dr. Surendra Vada and Mr. T Haribabu M.Pharm., PhD, have supported the analysis of the data., Mrs. Nageena, Mrs. Gayathri, Mrs. Jyotsna S Kharvi, Ms. N K Thanuja and Dr. Ranjith Muniswamy have pre-reviewed the article.

Funding Statement: none

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

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