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HOW CAN SUGAR DISEASE DISTURB THE FEET AND CAUSES FOOT ULCERS? *("HEALTHY LEGS ARE INDICATORS OF HEALTHY LIFE")*

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ABSTRACT

Diabetic foot refers to a condition in chronic diabetic individuals where neuropathy changes affect the foot due to neurological or vascular pathologies or both, causing complete loss of sensations which may lead to the development of ulcers in the foot associated with many life-threatening complications. Over time, high blood glucose levels and high levels of fat (triglycerides) can damage nerves. High blood glucose levels can also damage the small blood vessels that nourish the nerves with oxygen and nutrients. Type 2 diabetes has been found to affect a fourth of those with the condition, who are at high risk of developing foot problems that could lead to serious complications and amputations. Diabetic foot refers to foot problems, like diabetic foot ulcers and Charcot's foot, that are common in people with diabetes due to nerve damage (Diabetic neuropathy) and poor circulation. High blood sugar damages nerves and blood vessels, leading to loss of sensation, increased risk of injury, and slower healing. Research has been focused on mechanisms of diabetic neuropathy, but treatment options to eliminate the initial causes are still be short of. The impaired glucose metabolism in diabetes leads to hypoxia and acidosis, which trigger other abnormalities responsible for mitochondrial and bioenergetic dysfunction by increasing ROS production to cause membrane hyperexcitability and a reduction of ATP production. Diabetic foot ulceration is a devastating complication of diabetes that is associated with infection, amputation, and death, and is affecting increasing numbers of patients with diabetes mellitus.

KEYWORDS: Diabetes, Diabetes foot ulceration, Classification, Diabetes complications, Clinical management.

INTRODUCTION

Delays in access to specialist care appear to worsen ulcer severity and lead to an increase in amputation.[1]

Patients with diabetes mellitus (type 1 or 2) have a total lifetime risk of a diabetic foot ulcer complication as high as 25%.[2]

The suffering of affected individuals and the cost of DFUs are both equally staggering. Those individuals with DFUs usually have other complications of diabetes, including nephropathy. Data from the UK and the USA confirmed that the outlook for those people with foot complications who are on dialysis is very poor, with a high mortality risk.[3]

Data from our group confirm that those people with diabetes who have had an amputation and who are on dialysis have a 75% two-year mortality; the majority of these were of cardiovascular etiology. Data such as these are worse than most malignant diseases, with the possible exception of lung and pancreas. There is therefore an urgent need for preventative strategies to reduce the incidence of foot complications amongst those with diabetes.[4]

More recently, data from the UK in 2019 suggest that a conservative estimate of the annual cost of diabetic foot problems exceeds UK £900 million, which represents approximately 1% of the total budget of the National Health Service.[5]

The importance of regular diabetic foot care in very high-risk patients is emphasized by an observational study from Arizona, where the State decided to remove routine podiatry from high-risk patients to reduce their health budget.[6]

The etiopathogenesis will then be described, and aspects of management of neuropathic, neuroischemic, and infected DFUs considered.[7]

The question of how to address primary and secondary prevention of diabetic foot problems will then be discussed, followed by a section on Charcot neuroarthropathy.[8]

Diabetic foot ulcers (DFU) are common clinical problems and devastating complications of diabetes, and affect 15% of all diabetic patients and resulting in significant morbidity, mortality, and financial burdens.[9]

Five-year risk of mortality for a patient with a diabetic foot ulcer is 2.5 times higher than the risk for a patient without.[10]

Approximately 20% of moderate or severe DFU could cause some level of amputation. Moreover, 74% of them also have a risk of renal replacement therapy at 2 years.[11]

This high mortality rate is also related to coexisting comorbidities such as cardiovascular or cerebrovascular diseases. The pathophysiology of DFU is based on a triad of neuropathy, peripheral arterial disease, and concomitant secondary bacterial infection. Peripheral neuropathy could lead to intrinsic muscle atrophy and functional anatomical changes in the foot.[12]

Eventually, progressive secondary foot infection penetrating deep fascia, tendons, and joints could develop with repetitive inattention trauma. Infection could play a significant role in half of the major lower limb extremity amputations.[13]

Recent studies indicate some risk factors for the development of DFU. These are as follows: Longer than 10 years of duration of diabetes, male gender, older patients, presence of comorbidities including nephropathy, neuropathy, and peripheral vascular disease, and history of foot ulceration.[14]

The treatment of DFU requires an immediate decision and systematic approach that comprises of maintaining arterial blood flow, treating the infection appropriately, and removing the pressure from the wound.[15]

During the past 10 years, there has been an increasing amount of novel, basic science-based approaches and developments for adjuvant therapies, including wound dressing, hyperbaric oxygen therapy, or growth factor formulations for efficient local delivery.[16]

Diabetic foot is known as a set of syndromes in which neuropathy, ischemia, and infection cause tissue alterations or ulcers secondary to microtrauma. When talking about diabetic foot, we refer to a foot that has wounds or ulcers, typical of a person with diabetes. It arises from a dysfunction of the peripheral nerves in this type of patient.[17]

Diabetic foot harms diabetic patients throughout their lives and is an important complication that worsens the patient's clinical condition, in addition to reducing their quality of life and producing a great socioeconomic impact. The existing probabilities of amputation of a limb in diabetic patients are high.[18]

Diabetic foot is defined as the infection, ulceration or destruction of the deep tissues of the foot, located in the lower extremities and related to neuropathy or peripheral arterial disease. Foot complications are the most costly and serious of DM; on the other hand, they involve more hospitalizations than any other complication.[19]

There are also a few complementary therapies that have had positive results, such as hyperbaric oxygen therapy, the use of advanced wound-healing products, and negative-pressure wound therapy (TPWT).[20]

History

Marchal de Calvi and Thomas [Pryce/Hodgkin] are associated with the early understanding of the diabetic foot, with Calvi and Pryce establishing the connection between diabetes, nerve damage, and foot ulcers in 1864 and 1887, respectively, and Calvi and Hodgkin associating diabetes with foot gangrene in the 1850s. Their work established the relationship between diabetes and foot complications like neuropathy and gangrene, laying the groundwork for modern understanding and management of the condition.

Marchal de Calvi (in the 1860s): Described the signs of diabetic neuropathy for the first time. It was demonstrated that diabetes caused gangrene and infections in the lower limbs. It was identified that arterial calcifications and sensory disturbances developed as consequences of diabetes.

Thomas Pryce (in the 1880s): Along with Calvi and Rollo, firmly established the relationship between diabetes, peripheral nerve dysfunction, and foot ulceration.

Thomas Hodgkin(in the 1850s): First identified the association between diabetes, foot ulceration, and potential infection, which were significant sources of morbidity and mortality.

Their combined work was crucial in establishing a causal link. They showed that diabetes was the underlying cause of foot problems, not a consequence of them.

Study sugar, save the foot

Diabetic foot ulcer is a devastating complication of diabetes mellitus and a significant cause of mortality and morbidity all over the world, and can be complex and costly. Diabetic foot problems are going to reach epidemic proportions in the country in the next few years, and most patients will be in the age group of 35-45. The conditions develop due to high glycemic levels for prolonged periods, which causes pathological changes in peripheral nerves, blood vessels, or both.

Why do diabetics get foot ulcers?

High blood sugar levels activate an enzyme called Aldose Reductase, which leads to the accumulation of sorbitol and fructose in nerves. Macrophages infiltrating the peripheral nerves release cytokines and chemokines, promoting inflammation and damaging nerve fibers. The accumulation of these substances results in non-enzymatic glycosylation (glycation) of structural nerve proteins, further impairing their function. Metabolic imbalances can lead to dysfunction of the mitochondria within nerve cells, and insulin signaling can inhibit the ability of nerves to repair themselves after injury.

Types of Diabetic Foot

1) Purely neurological (35%)
2) Purely vascular (Endo neural hypoxia) (15%)
3) Combined, i.e, involves both nerves & blood vessels (50%).

Why Foot Ulcers Are Dangerous

1) PURELY NEUROLOGICAL COURSES:

(A) Enzymatic causes

High blood sugar levels activate an enzyme called Aldose Reductase, which leads to the accumulation of sorbitol & fructose in nerves cells.

(B) Cellular & inflammatory process

Macrophages infiltrating the peripheral nerves release cytokines and chemokines, promoting inflammation & damaging nerve fibers.

(C) Mitochondrial Dysfunction

Metabolic imbalances can lead to dysfunction of the mitochondria within nerve cells. These metabolic & inflammatory pathways collectively cause damage to the entire peripheral nervous system, including nerve Axons & surrounding Glial cells.

(D) Impaired nerve repair after injury

Inhibition of repair: Aberration in insulin signaling can inhibit the ability of nerves to repair themselves after injury.

(E) Apoptosis

These processes can promote programmed cell death (Apoptosis) in damaged nerve cells.

(F) Other diseases that cause damage to the myelin sheath include

(i) Guillain-Barré syndrome (G.B.Syndrome)

(ii) Chronic inflammatory demyelinating polyradiculopathy

(iii) Para proteinemic demyelinating neuropathy

(iv) Charcot-Marie-Tooth type 1 & type X

(v) Copper deficiency

(vi) Autoimmune diseases:

The most common neurological autoimmune disease is multiple sclerosis (MS). In MS, the body's immune system mistakenly attacks and damages the protective myelin sheath that covers the nerve fibers (in the central nervous system). This damage disrupts the signals between the brain & the body, leading to symptoms like defective vision, imbalances, difficulty in coordination & numbness or weakness in different parts of the body.

(vii) Myasthenia Gravis

(viii) Neuromyelitis optica

(ix) Role of methylcobalamin, which can modulate neuroinflammatory cytokines, promote nerve regeneration and remyelination & protect against oxidative stress, offering a potential therapeutic role in managing diabetic neuropathy symptoms & improving nerve function.

The deficiency of this may impair nerve regeneration.

The role of methylcobalamin (vit B12) can potentially help to mitigate these effects with some of its potential roles in – Anti-inflammatory effects by reducing pro – pro-inflammatory cytokines, regulate inflammatory responses & protect nerves from inflammation-related damage.

It promotes the regrowth & repair of injured nerves & supports the thickness & density of the myelin sheath by activating processes related to the nerve outgrowth & myelin synthesis.

Ø Anti-oxidant effects by protecting nerve cells from damage.

Ø Improves nerve conduction: It helps to restore normal nerve function, improving nerve conduction velocity.

Ø Alleviating symptoms: Methyl cobalamin has been shown to relieve symptoms of diabetic neuropathy, including pain & weakness.

How common is diabetic neurology?

Many studies suggest that approximately one-half of people with diabetes have peripheral neuropathy. More than 30% of people with diabetes have autonomic neuropathy.

(2) PURELY VASCULAR TYPE

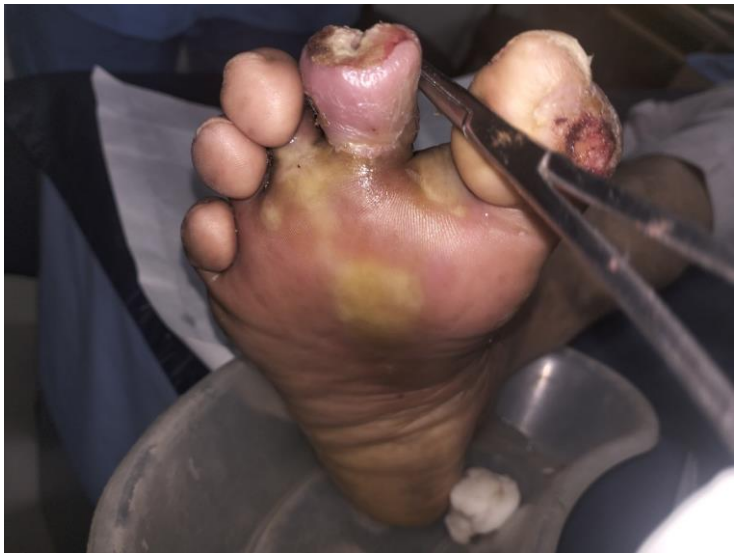
Also called Ischemic foot is caused by peripheral arterial disease (PAD) due to narrowed or blocked arteries rather than nerve damage. These ulcers often appear as irregular, pale, or necrotic lesions, sometimes with gangrene. They are more common on the dorsal surfaces of the toes and other areas of Ischaemia. High blood sugar levels can affect the endothelium of both arteries & veins and reduce the production of nitric oxide, a molecule essential for vasodilation. In case of arteries, it causes thickening & stiffness of intima & plaque formations (atherosclerosis with calcium deposits) which reduces the compliance & luminal diameter, thereby decreasing blood flow to the extremities,

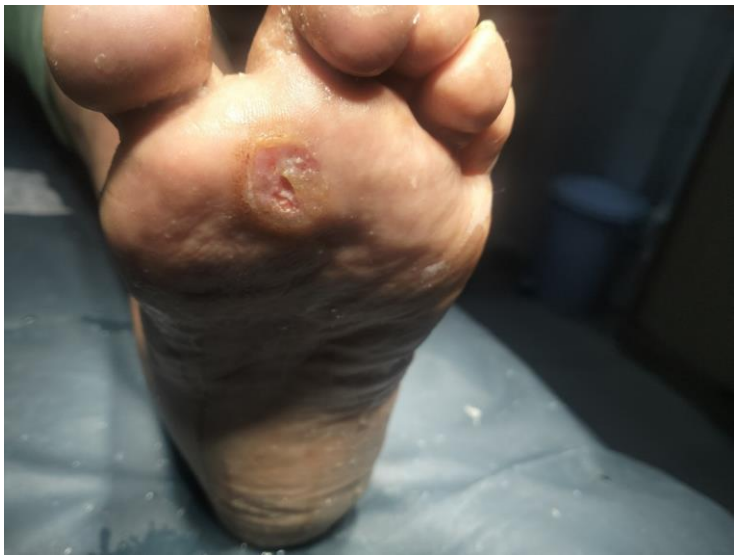
impacting oxygen delivery to organs and tissues. Whereas the endothelium damage in veins leads to decreased nitric oxide (NO) production. This also affects the contractile efficiency of the venous wall, thereby reducing the venous return to the heart.

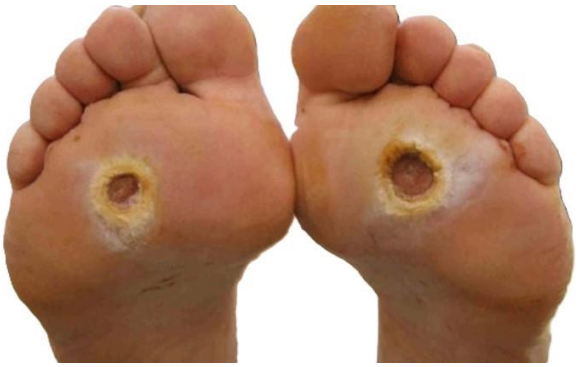
Endothelium damage from diabetes leads to venous insufficiency by promoting inflammation, oxidative stress, and the breakdown of extracellular matrix (ECM) proteins within the vein walls & valves, & walls thereby weakening the structural integrity of the veins.

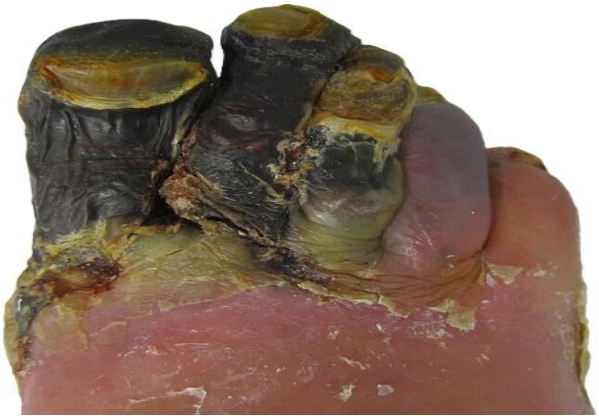
Microvascular dysfunction occurs due to prolonged exposure to high glucose, which damages the small blood vessels, as well as contributing to reduced tissue perfusion.

This damage also reduces nitric oxide (NO) production, impairing the vascular relaxation & blood flow, and increases adhesion molecules, which promote clotting and inflammation. These combined effects result in weakening of the veins and damage to valves that cannot effectively carron venous return to the heart, causing blood to pool in the legs, leading to oedema.

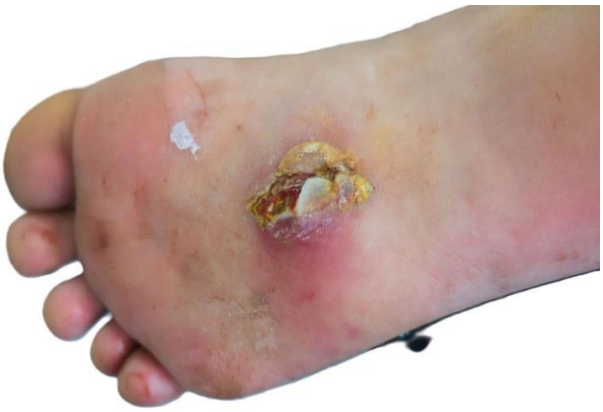






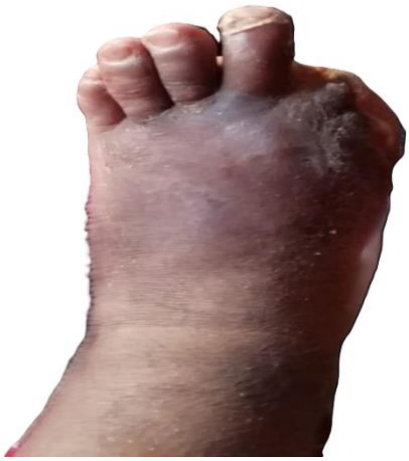


FORE FOOT GANGRENE



DIABETIC FOOT ULCER

DIABETIC FOOT ULCER PREGANGRENOUS CHANGES



AMPUTATION OF BIG TOE WITH PRE GANGRENOUS CHANGES OF FOOT

Clinical manifestations

Early features comprise

- Tingling and numbness in the soles of the foot.
- Mild pain
- Burning sensations
- Decreased sensations
- Shiny skin (early subcutaneous oedema)
- Cracked heels
- loss of hair
- Ulcers
- Late Features:
- Complete loss of sensations
- Swelling in legs
- Blister formations(water logged cysts)
- Discolouration of skin in the toes/foot
- Fungal infections in the foot.
- Non-healing ulcers
- Decreased local temperature/cold & clammy skin
- Increased sweating
- Pre-Gangrenous/Gangrenous changes

Stages of neuropathy

Stage - 0: No symptoms

Stage - 1: On & off pain & numbness

Stage - 2: Above symptoms are regular & persistent, which interfere with daily routine

Stage - 3: Peaks of pain

Stage - 4: Constant numbness

Stage - 5: Complete loss of sensations

Classification of Diabetic foot

Diabetic foot is classified using systems like the Wagner grading system, which assesses ulcer depth and tissue involvement from 0 (pre-ulcerative) to 5 (full-foot gangrene). Another system, the University of Texas (UT) wound classification, grades ulcers by depth and also incorporates stages based on infection and ischemia (lack of blood flow). Other systems, such as the International Working Group on the Diabetic Foot (IWGDF) classification, focus on infection severity and risk factors for developing ulcers.

WAGNER GRADING SYSTEM

This system primarily assesses the severity and depth of a diabetic foot ulcer.

Grade 0: Intact skin, pre-ulcerative lesion, or post-ulcerative lesion.

Grade 1: Superficial ulcer, involving skin and subcutaneous tissue.

Grade 2: Deep ulcer extending to tendon, muscle, or bone.

Grade 3: Deep ulcer with abscess, osteomyelitis (bone infection), or joint sepsis.

Grade 4: Gangrene involving a portion of the foot(forefoot).

Grade 5: Gangrene involving the entire foot.

UNIVERSITY OF TEXAS (UT) WOUND CLASSIFICATION

This is a more detailed system that considers depth, infection, and ischemia.

Grades assess depth

Grade 0: Pre- or post-ulcerative site.

Grade 1: Superficial wound not involving tendon, capsule, or bone.

Grade 2: Wound penetrates to tendon or capsule.

Grade 3: Wound penetrates bone or joint.

Stages assess infection and ischemia

Stage A: Clean wounds.

Stage B: Non-ischemic infected wounds.

Stage C: Ischemic non-infected wounds.

Stage D: Ischemic infected wounds.

Other Classification Considerations

IWGDF Classification

Divides foot ulcers into infection grades (uninfected, mild, moderate, severe).

PEDIS System

Another system that classifies ulcers by Perfusion, Extent/size, Depth/tissue loss, Infection, and Sensation.

Modified American Diabetes Association (ADA) Risk Classification:

Categorizes patients based on their risk of developing diabetic foot complications.

Is neuropathy reversible?

Neuropathy is an irreversible process

Life after established neuropathy of the foot:

With Diabetes mellitus - 10.8 years.

Without Diabetes mellitus - 13.9 years.

Treatment

Which aims at strict glycemic control with regular & proper monitoring by the team constituting -

1) Diabetologist

2) Endovascular surgeon

3) Neurologist &

4) Surgeon

Several factors contribute to the formation of DFU

Metabolic disorders, chronic inflammation, endothelial injury and proliferation, and microvascular haemorrhage are responsible contribute to the formation of DFU.[22]

In addition to abnormal glucose metabolism, diabetic patients often have lipid metabolism disorders, which promote the release of inflammatory mediators, leading to the infiltration of immune cells.[23]

The immune system regulates inflammation and strives to maintain internal balance. Diabetes sustains a persistent pro-inflammatory environment and modulates abnormal immune cell expression.[24]

Although glycaemic control, physical therapy and antibiotic treatment are currently the main treatment approaches, these methods are not always effective.[25]

For established ulcers, especially in individuals whose immune system is already compromised, treatment is even more challenging.

Unfortunately, even after effective wound healing, the recurrence rate of DFUs is very high.

Unfortunately, even after effective wound healing, the recurrence rate of DFUs is very high.[26]

Molecular immunology of wound healing

The body’s immune system is actively involved in response to an injury. Some of the major immune cells involved in the wound healing process are platelets, macrophages, neutrophils, and lymphocytes (natural killer cells, B and T cells). Diabetic foot ulcer (DFU) is a leading cause of amputation in diabetic patients. Consequences of DFU include infections, decline in limb function, hospitalization, amputation, and, in severe cases, death. Immune cells, including macrophages, regulatory T cells, fibroblasts, and other damage repair cells, work in sync for effective healing and in the establishment of a healthy skin barrier post-injury. Immune dysregulation during the healing of wounds can result in wound chronicity. Hyperglycemic conditions in diabetic patients influence the pathophysiology of wounds by disrupting the immune system as well as promoting neuropathy and ischemic conditions, making them difficult to heal. Chronic wound microenvironment is characterized by increased expression of matrix metalloproteinases, reactive oxygen species, as well as pro-inflammatory cytokines, resulting in persistent inflammation and delayed healing.[27]

Mysterious malady strikes the diabetic Foot

Diabetic foot ulcers (DFU) are common clinical problems and devastating complications of diabetes, affecting 15% of all diabetic patients and resulting in significant morbidity, mortality, and financial burdens Five-year risk of mortality for a patient with a diabetic foot ulcer is 2.5 times higher. Approximately 20% of moderate or severe DFU could cause some level of amputation. Moreover, 74% of them also have a risk of renal replacement therapy at 2 years.

IMPORTANT LIFE SAVING PRECAUTIONS (WHO GULDLINES)

While there aren't specific, distinct "WHO guidelines" for diabetic foot prevention, the World Health Organization (WHO) promotes an overall approach to diabetes management that indirectly covers foot care, with detailed evidence-based prevention strategies primarily provided by expert groups like the International Working Group on the Diabetic Foot (IWGDF).

Key Prevention Strategies

These strategies, supported by expert bodies like the IWGDF, form the core of diabetic foot prevention.

Daily Foot Self-Care

Inspect feet daily: Look for cuts, blisters, redness, swelling, or any changes, paying close attention to between the toes.

Wash feet daily: Use warm (not hot) water and dry thoroughly by blotting or patting, especially between the toes.

Moisturize dry skin: Apply a gentle emollient to prevent cracking, but avoid applying it between the toes.

Care for toenails: Trim toenails straight across and file sharp edges.

Never go barefoot: Always wear well-fitting shoes and socks or slippers to protect your feet, even indoors.

Appropriate Footwear

Wear proper-fitting shoes: Choose shoes with a wide toe box and sufficient depth to avoid pressure points.

Use therapeutic footwear: For moderate-to-high-risk individuals, wear footwear designed to relieve pressure and prevent ulcer recurrence.

Patient and Provider Education

Educate patients: Provide structured education on foot self-care, safe practices, and risk factors for foot problems.

Educate caregivers: Ensure family members and healthcare providers understand the principles of diabetic foot prevention.

Professional Foot Care

Regular foot exams: Have your healthcare provider perform regular foot inspections and examinations to identify at-risk individuals and monitor foot health.

Risk assessment: Use established risk stratification tools to assess ulcer risk and determine the frequency of foot examinations.

Addressing Risk Factors

Treat calluses and corns safely: Do not use chemical agents or plasters; consult a healthcare professional on safe removal methods.

Manage underlying conditions: Control blood glucose levels and address any other risk factors for foot complications.

Multidisciplinary Care

Team approach: For moderate-to-high-risk patients, an integrated team approach involving Endocrinologists, Endovascular surgeon, Neurologist, and Surgeon (if required) is recommended for comprehensive foot care.

NEW DIABETES GUIDELINES

The American Diabetes Association's 2025 Standards of Care emphasize comprehensive lifestyle interventions, personalized glycemic goals, and early use of newer pharmacologic agents. For type 1 diabetes, this includes continuous glucose monitoring and automated insulin delivery systems. For type 2 diabetes, guidelines focus on lifestyle changes like diet and exercise, weight management, and the use of medications like GLP-1 receptor agonists to reduce cardiovascular risk and promote weight loss. Screening for comorbidities and complications is a key component, alongside education, self-management support, and addressing psychosocial factors like sleep.

Key Aspects of Current Guidelines

Personalized Care

Guidelines stress individualized treatment plans and goals, factoring in a patient's age, comorbidities, and lifestyle.

Lifestyle Interventions

Diet

Dietitian, emphasize the inclusive food-based eating patterns with healthy fats.

Exercise

Recommends at least 150 minutes of moderate-intensity aerobic exercise weekly and two or more resistance training sessions per week.

Weight Management: Crucial for improving blood glucose and blood pressure in type 2 diabetes.

Sleep

Prioritizing 7-9 hours of quality sleep is recommended to support blood sugar regulation and hormonal balance.

Glycemic Management

Type 1 Diabetes: Early use of continuous glucose monitoring, automated insulin delivery systems, and education on insulin-to-carb matching are recommended.

Type 2 Diabetes: Goal setting and pharmacological management using medications like semaglutide and tirzepatide for those with cardiovascular disease or the goal of weight loss are emphasized.

Comorbidity Screening

Routine screening for and prompt treatment of cardiovascular risk factors (hypertension, hyperlipidemia) and microvascular complications (retinopathy, neuropathy, nephropathy) are recommended.

Psychosocial Support

Diabetes self-management education and support are essential components of care, as are addressing factors like sleep, which can impact blood sugar control.

FUTURE RESEARCH DIRECTIONS

The complexity of the wound repair process itself, particularly from molecular, cellular, and physiological perspectives, coupled with the intricacy of diabetic, cardiovascular patients, mandates a multidisciplinary approach both in the clinical setting as well as in the research realm. Although more sophisticated technologies, such as single-cell or spatial "omics" and big data analytics of artificial intelligence, are being used, there are major gaps in all research areas that translate into the absence of effective treatments that are critically needed for this increasing patient population. Current views on diabetic foot ulcers (DFUs) emphasize a multifaceted approach that involves robust wound care, advanced therapies such as negative pressure wound therapy and specialized dressings, diligent management of infection and ischemia, and comprehensive, patient-centered care to prevent amputation and mortality, which remain high despite advances. For established ulcers, especially in individuals whose immune system is already compromised, treatment is even more challenging.

CONCLUSION

This study highlights the factors that contribute to DFU, the complexity of the wound repair process, and the crucial role of CD8 T cells, which play a significant immunoregulatory role in the healing process of DFU. Metabolic disorders, chronic inflammation, endothelial injury, proliferation, and microvascular haemorrhage are responsible in the formation of DFU. Advancements like continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems are integrated, especially for type 1 diabetes, to improve glycaemic outcomes and quality of life. Food choices in both the prevention and management of diabetes, as dietary habits exert a direct influence on blood glucose regulation and long-term health outcomes. A balanced intake of whole grains, legumes, fruits, and vegetables consistently demonstrates protective effects, whereas processed foods and refined sugars are strongly associated with glycemic variability and complications. Culturally sensitive dietary guidance enhances patient adherence, particularly when traditional diets are integrated with modern nutritional science, offering a promising path for sustainable lifestyle modification. Personalized nutrition plans further optimize glycemic control and reduce risks, while awareness campaigns and structured education remain indispensable for empowering patients. At the community level, targeted programs can bridge knowledge gaps among vulnerable groups, reinforcing the message that food plays a central role in disease control. Multidisciplinary care involving physicians, dietitians, and allied health professionals has been shown to strengthen outcomes, and continued research into regional food patterns will add depth to existing guidelines. Ultimately, healthier food choices empower individuals to take control of their condition, underscoring that a food-centered approach serves as both a preventive and therapeutic cornerstone in diabetes care.

REFERENCES

1. NHS Digital. National Diabetes Foot Care Audit Fourth Annual Report: England and Wales, 01 April 2015 to 31 March 2018. Available at: https://files.digital.nhs.uk/FC/18ED7F/NDFA%204AR%20-%20Main%20Report%20v1.1.pdf Last accessed 1 May 2020. [Google Scholar]
2. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, LeMaster JW, Mills JL, Mueller MJ, Sheehan P, Wukich DK. Comprehensive foot examination and risk assessment. A report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Phys Ther, 2008 Nov; 88(11): 1436-43. [PubMed]

3. Lavery LA, Hunt NA, Ndip A, et al. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care, 2010; 33: 2365-2369. [PMC free article] [PubMed]
4. Rogers LC, Lavery LA, Armstrong DG. The right to bear legs. J Am Podiatr Med Assoc, 2008; 98: 166-168. [PubMed]
5. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabetic Med, 2019; 36: 995-1002. [PubMed]
6. Skrepnek GH, Mills JL, Armstrong DG. Foot-in-Wallet Disease: tripped up by "cost-saving" reductions? Diabetes Care, 2014; 37: 196-197. [PubMed]
7. Boulton AJM. The diabetic lower limb – a forty-year journey: from clinical observation to clinical Science. Diabetic Medicine, 2019; 36: 1539-1549. Doi.org/10.1111/dme.13901. [PubMed]
8. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. New Engl J Med 2017; 376: 2367-2375. [PubMed]
9. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis †. Ann Med, 2017; 49: 106-116. [RCA] [PubMed] [DOI] [Full Text] [Cited by in Crossref: 666] [Cited by in RCA: 985] [Article Influence: 123.1] [Reference Citation Analysis (5)
10. International Diabetes Federation. Diabetes Atlas. 7th ed. Brussels, Available from: http:// www.diabetesatlas.org, 2015. [DOI] [Full Text]
11. Guariguata L. By the numbers: new estimates from the IDF Diabetes Atlas Update for 2012. Diabetes Res Clin Pract, 2012; 98: 524-525. [RCA] [PubMed] [DOI] [Full Text] [Cited by in Crossref: 115] [Cited by in RCA: 115] [Article Influence: 8.8] [Reference Citation Analysis (0)]
12. Khanolkar MP, Bain SC, Stephens JW. The diabetic foot. QJM, 2008; 101: 685-695. [RCA] [PubMed] [DOI] [Full Text] [Cited by in Crossref: 95] [Cited by in RCA: 99] [Article Influence: 5.8] [Reference Citation Analysis (1)]
13. Robinson BV. The pharmacology of phagocytosis. Rheumatol Rehabil, 1978; Suppl: 37-46. [RCA] [PubMed] [DOI] [Full Text] [Cited by in Crossref: 4] [Cited by in RCA: 4] [Article Influence: 0.1] [Reference Citation Analysis (0)]
14. Waaijman R, de Haart M, Arts ML, Wever D, Verlouw AJ, Nollet F, Bus SA. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care, 2014; 37: 1697-1705. [RCA] [PubMed] [DOI] [Full Text] [Cited by in Crossref: 159] [Cited by in RCA: 167] [Article Influence: 15.2] [Reference Citation Analysis (1)]
15. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower-extremity amputation in patients with diabetes. Diabetes Care, 2008; 31: 1331-1336. [RCA] [PubMed] [DOI] [Full Text] [Full Text (PDF)] [Cited by in Crossref: 133] [Cited by in RCA: 146] [Article Influence: 8.6] [Reference Citation Analysis (0)]
16. Harries RL, Harding KG. Management of diabetic foot ulcers. Curr Geriatr Ref, 2015; 4: 265-276.
17. Akkus G, Sert M. Diabetic foot ulcers: A devastating complication of diabetes mellitus continues non-stop despite new medical treatment modalities. *World J Diabetes* 2022; 13(12): 1106-1121 [PMID: 36578865 DOI: 10.4239/wjd.v13.i12.1106]
18. Seguel, G. Why should we worry about diabetic foot? Importance of the diabetic foot. *Scielo*, 2013; *141*: 1–3. Available

online: https://scielo.conicyt.cl/scielo.php?pid=S003498872013001100014&script=sci_arttext&tlng=en (accessed on 10 February 2022).

19. Paiva, M.O.; Rojas, S.N. Diabetic foot. Can we prevent it? *Rev. Med. Clin. Condes*, 2016; *27:* 227–234. Available online: https://reader.elsevier.com/reader/sd/pii/S0716864016300128?token=89C76D7368B0329DA83F2219FCB151C7CBD0D5F2AB1D67524028056B8070B14CBE17C1365FA150C99E35B2FBB6A30760&originRegion=eu-west-1&originCreation=20211202143657 (accessed on 10 February 2022)
20. Rincón, Y.; Gil, V.; Pacheco, J.; Benítez, I.; Sánchez, M. Diabetic foot evaluation and treatment. *Scielo*, 2012; *10*: 1–5. Available online:http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S1690-31102012000300008 (accessed on 10 February 2022).
21. Yu X, Liu P, Li Z, Zhang Z. Function and mechanism of mesenchymal stem cells in the healing of diabetic foot wounds. Front Endocrinol (Lausanne), 2023; 14: 1099310. [DOI] [PMC free article] [PubMed] [Google Scholar]
22. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Front Immunol, 2020; 11: 1582. [DOI] [PMC free article] [PubMed] [Google Scholar]
23. Song J, Hu L, Liu B, et al. The emerging role of immune cells and targeted therapeutic strategies in diabetic wounds healing. J Inflamm Res, 2022; 15: 4119-4138. [DOI] [PMC free article] [PubMed] [Google Scholar]
24. Baig MS, Banu A, Zehravi M, et al. An overview of diabetic foot ulcers and associated problems with special emphasis on treatments with antimicrobials. Life (Basel), 2022; 12(7): 1054. [DOI] [PMC free article] [PubMed] [Google Scholar]
25. Lin S, Wang Q, Huang X, et al. Wounds under diabetic milieu: the role of immune cellar components and signaling pathways. Biomed Pharmacother, 2023; 157: 114052. [DOI] [PubMed] [Google Scholar]
26. Matijevic T, Talapko J, Mestrovic T, et al. Understanding the multifaceted etiopathogenesis of foot complications in individuals with diabetes. World J Clin Cases, 2023; 11(8): 1669-1683. [DOI] [PMC free article] [PubMed] [Google Scholar]
27. Fatima Mohsin 1, Sheza Javaid 2, Mishal Tariq 3, Muhammad Mustafa, Molecular immunological mechanisms of impaired wound healing in diabetic foot ulcers (DFU), current therapeutic strategies and future directions, Int Immunopharmacol, 2024 Sep 30; 139: 112713,doi: 10.1016/j.intimp.2024.112713. Epub 2024 Jul 23.