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NEURODEGENERATIVE DIABETES: A LEADING IMPLICATION OF ALTERED PATHOPHYSIOLOGICAL MECHANISMS IN FOOT

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ABSTRACT

Diabetic neuropathy is a progressive neurodegenerative disorder specifically affecting the peripheral nervous system, is a major complication of diabetes mellitus. This condition primarily damages sensory and autonomic nerve fibers, and later to a lesser extent, motor axons. This review aims to explore the complicated pathophysiology of diabetic neuropathy leading to foot nerve damage followed by ulcer formation and then progression to cancer. We address the interaction between ischemia, inflammation, metabolic and oxidative stress, and reduced neurotrophic support in nerve damage. There is discussion of the mechanisms underlying the creation of ulcers, including diminished healing and loss of protective feeling. Additionally, we look on the possible development of malignancy, specifically squamous cell carcinoma and Marjolin's ulcer, from long-term diabetic foot ulcers. The review ends with a summary of the current approaches to managing diabetic foot ulcers, which include sophisticated therapies like hyperbaric oxygen and reconstructive surgery, as well as blood glucose control and wound care interventions. This thorough review emphasizes the complexity of diabetic neuropathy and its consequences for the foot, underscoring the necessity of multidisciplinary treatment and early intervention to enhance patient outcomes.

KEYWORDS: Diabetic, Neuropathy, Neurodegenerative, Ulcer, Oxidative Stress.

INTRODUCTION

Due to its dependence on daily fluctuations in diet, exercise, illness, and stress, diabetes necessitates a lifelong management approach that incorporates these variable factors. As the

patient is in the most advantageous position to monitor these daily changes, a comprehensive understanding of the disease and its impact on normal bodily functions is crucial. Furthermore, awareness of diabetes, its potential complications, and advancements in healthcare have been demonstrably linked to improved long-term prognoses.[1] Since dietary management is intricately linked to diabetes control, a strong foundation in food science, nutrition, and the underlying principles of biochemistry, physiology, and disease development empowers patients to effectively understand and manage this condition. "Diabetes mellitus, characterized by excessive urination (Glycosuria), is a leading global cause of both morbidity (Illness)[2] and mortality (Death). The term originates from the Greek word 'diabanein,' signifying 'to pass through,' referencing the prominent symptom of the disease."[3] Diabetes mellitus can be broadly classified into three main types: type 1, type 2, and gestational diabetes. Type 1 diabetes mellitus is characterized by a deficiency in insulin production due to the destruction of insulin-producing beta cells in the pancreatic islets of Langerhans. This form can be further subcategorized as immune-mediated or idiopathic.[4] Type 2 diabetes mellitus, formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is a metabolic disorder defined by elevated blood glucose levels in the presence of both insulin resistance and relative insulin deficiency.[5] Gestational diabetes mellitus is a specific type of diabetes that develops in non-diabetic women during pregnancy, typically arising in the late third or early fourth trimester. This condition typically resolves postpartum and is characterized by altered glucose utilization within the body.[6]

Diabetic neuropathy is a progressive neurodegenerative disorder specifically affecting the peripheral nervous system. This condition primarily damages sensory and autonomic nerve fibers, and later to a lesser extent, motor axons. The exact cause of this damage in sensory neurons is under debate. As diabetic neuropathy progresses, the farthest sensory nerve endings in the limbs begin to degenerate and retract, while the cell bodies remain relatively unharmed. This pattern of damage, resembling a stocking and glove, signifies that the longest nerve axons are affected first. Consequently, diabetic neuropathy is classified as a length-dependent neuropathy. While substantial evidence suggests that the entire length of the neuron is susceptible to diabetic damage, the initial site of injury remains unclear. Debate surrounds whether the damage begins in the peripheral axons and Schwann cells, or originates in the cell bodies located within the dorsal root ganglia. Despite diabetic neuropathy being classified as primarily non-demyelinating, chronic high blood sugar

(Hyperglycaemia) damages Schwann cells, and in advanced cases, demyelinating features can be observed in some patients.[7-9]

Patterns of nerve injury in diabetic neuropathy

Diabetic neuropathy can manifest in several different patterns, each with varying characteristics. Diabetic neuropathy presents in a spectrum of patterns, with distal symmetric polyneuropathy, characterized by progressive sensory and motor deficits beginning in the distal lower extremities, being the most common. Other patterns include small-fiber predominant neuropathy, which shares a similar distribution but affects pain and autonomic fibers, and diabetic radiculoplexopathy or radiculopathy, which can improve with immunotherapy unlike most diabetic neuropathies. Mononeuropathy affects a single nerve, while autonomic neuropathy disrupts involuntary functions. Treatment-induced neuropathy, often unrecognized, can arise from aggressive blood sugar management and mimic various presentations. Accurate diagnosis through comprehensive evaluation is essential for guiding management and preventing further nerve damage.[10]

Clinical manifestations of diabetes neuropathy

In the vast majority of diabetic neuropathy cases, a doctor can arrive at a diagnosis simply by reviewing the patient's medical history and conducting a physical examination.[11] Diabetic neuropathy is diagnosed based on symptoms, clinical examination, and sometimes tests to rule out other causes. Patients typically experience numbness, tingling, pain, weakness, and unsteadiness in the feet and legs that can progress upwards.[12] Doctors assess sensation using tools like tuning forks and examine reflexes to detect nerve damage. While objective tests like nerve conduction studies (NCS) can provide additional evidence, the diagnosis often relies solely on the patient's history and physical exam. NCS measure nerve function and are abnormal in many diabetic neuropathy cases, but may be normal for small fiber neuropathy which presents with burning pain.[13,14] Skin biopsies are the gold standard for diagnosing small fiber neuropathy but are rarely used in routine diagnosis due to being invasive.[15] Atypical presentations like sudden onset, weakness, or asymmetry in symptoms warrant further investigation to rule out other conditions. This may involve blood tests, imaging studies, or even spinal fluid analysis.[16]

Mechanism of diabetic neuropathy leading to foot nerve damage

The widespread prevalence of prediabetes and diabetes worldwide has resulted in a parallel rise in the complications associated with these conditions. Among these complications,

neuropathy is the most common, with distal symmetric polyneuropathy (referred to as diabetic neuropathy in this context) being highly prevalent. Diabetic neuropathy is characterized by a gradual loss of sensory function starting from the extremities of the lower limbs, accompanied by pain and significant morbidity. It is a distinctive neurodegenerative disorder affecting the peripheral nervous system, primarily targeting sensory axons and autonomic axons, and to a lesser extent, motor axons at a later stage.[17]

Diabetic peripheral neuropathy is a complicated and multifaceted etiology that involves the interplay of vascular variables and metabolic abnormalities. Although hyperglycaemia is a known contributing factor, a number of other important factors have also been identified: toxic obesity, oxidative stress, mitochondrial dysfunction, polyol pathway activation, buildup of advanced glycation end products (AGEs), and increased markers of inflammation. Although the exact pathophysiological mechanisms remain unclear, it is believed that autoimmune, microvascular insufficiency, and disruptions in metabolic balance are involved.

It is thought that these methods impact the supporting glial cells as well as the peripheral sensory neurons. There has been evidence of metabolic abnormalities, including oxidative and nitrosative stress, altered calcium handling, elevated polyol pathway activity, with mitochondrial dysfunction. Degenerative alterations such as microvascular abnormalities, thickening of the basement membrane, proliferation of endothelial cells, and damage to both myelinated and unmyelinated fibers have been found in nerve biopsies. These peripheral lesions may eventually transmit signals to the central nervous system, which could cause nociceptive neurons to become centrally sensitized and contribute to the poorly understood phenomena of neuropathic pain and nerve injury (typically in leg and foot) in diabetes.[18,19] The underlying mechanics are outlined here:

Metabolic and Oxidative stress

Diabetic peripheral neuropathy (DPN) is characterized by nerve cell injury that is caused by oxidative stress, metabolic disturbances, and inflammatory processes that are mediated by several interrelated pathways. Peripheral nerve function can also be impacted by diseases of the central nervous system. Insulin resistance, dyslipidemia, hyperglycaemia, and microvascular abnormalities are the main contributing causes. Protein kinase C, polyol, advanced glycation end products, hexosamine, and poly (ADP-ribose) polymerase are among the pathways that are activated by hyperglycaemia and dyslipidemia; insulin resistance and microvascular diseases activate other harmful pathways. When these pathways come

together, they cause oxidative stress, inflammation, metabolic disruptions, and mitochondrial malfunction, which ultimately results in nerve damage.[20]

PKC (Protein kinase C) pathway

Elevated diacylglycerol levels in hyperglycaemia stimulate the conventional PKC isoforms (PKC-β, PKC-δ, and PKC-α) in cells. PKC activation modifies the expression of many target genes, including vasoconstrictor endothelin-1, TGF-β, and plasminogen activator inhibitor-1. It also decreases the expression of vasodilator nitric oxide synthase. PKC activation affects normal body metabolism and results in changes to vascular variables, insulin production, and other metabolic processes. By raising the generation of reactive oxygen species, decreasing glial cell viability, and decreasing glutamate absorption, PKC activation might result in oxidative damage. PKC inhibitors that specifically target isoforms such as PKC-β have demonstrated potential in mitigating neuropathic alterations in animal models, indicating that the PKC pathway may hold therapeutic promise in the treatment of diabetic neuropathy. In conclusion, metabolic disturbances, vascular anomalies, oxidative stress, and nerve injury are all mediated by hyperglycaemia-induced PKC pathway activation, which plays a role in the etiology of diabetic neuropathy.[21]

Advanced Glycation end Products (AGEs)

Advanced glycation end-products, or AGEs, are created when proteins, lipids, or nucleic acids undergo non-enzymatic glycation in diabetes because of hyperglycaemia. By raising reactive oxygen species, AGEs build up in peripheral neurons and encourage oxidative stress (ROS). This results in adverse gene alterations in the nerves, causes inflammation in the brain, and disrupts axonal transport and neuronal electrical activity. By binding to their receptor, known as the receptor of advanced glycation end products (receptor RAGE), AGEs exert their effects. Furthermore, the production of AGE and nerve injury are facilitated by the intracellular buildup of sorbitol resulting from the activation of the polyol pathway.

In conclusion, it is suggested that AGE buildup in nerves is a primary pathogenic mechanism causing oxidative stress, inflammation, & direct damage to neurons, all of which contribute to the onset and advancement of diabetic neuropathy.[22]

Polyol pathway

The polyol pathway triggers a series of metabolic processes that lead to diabetic neuropathy. In this process, aldose reductase uses NADPH as a cofactor to convert glucose to sorbitol,

and sorbitol dehydrogenase uses NAD to further metabolize sorbitol to fructose. The redox status of the cell is modified by this mechanism by adjusting the ratios of NADH/NAD+ and NADPH/NADP+. Because reduced glutathione (GSH) regeneration is a result of NADPH depletion, it is especially important as a scavenger of reactive oxygen species (ROS). The subsequent drop in GSH levels aggravates intracellular oxidative stress and adds to the problems associated with diabetes. The vasa nervorum, which supplies blood vessels to the nerves, experiences reduced blood flow and altered redox state as a result of this elevated oxidative stress. Therefore, increased oxidative stress and changed cellular redox state, which combined impact nerve function and blood flow to nerves, are the main ways in which the polyol pathway causes nerve damage in diabetic neuropathy.[23]

Hexosamine pathway

The hexosamine pathway, by a complicated cascade of metabolic changes, contributes significantly to diabetic neuropathy and nerve injury. This route involves the conversion of fructose-6-phosphate from glycolysis to glucosamine-6-phosphate, which is subsequently changed by glucosamine-6-phosphate amidotransferase into UDP-N-acetyl glucosamine (UDPGlcNAc). The generation of N-acetyl glucosamine (GlcNAc) as a result increases oxidative stress, which causes β-cell failure. Hyperglycaemia causes an increase in hydrogen peroxide, glucosamine-6-phosphate amidotransferase levels, and the expression of the glucokinase gene, glucose transporter 2, and insulin synthesis.

Moreover, the pathway modifies gene transcription factor Sp1, which impacts the expression of plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor β1 (TGF-β1). Increased production of collagen matrix is linked to endothelial fibrosis and suppression of mesangial cell proliferation when TGF-β1 is upregulated, and vascular smooth muscle cells are enhanced when PAI-1 is elevated, which is linked to the development of atherosclerosis. When combined, these pathways cause increased oxidative stress, changed gene expression, endothelial fibrosis, and vascular alterations that compromise nerve function and blood flow, ultimately resulting in nerve damage in diabetic neuropathy.[24,25]

Ischemia and Microvascular damage

Reduced brain blood flow, decreased intra-neural oxygen tension, and malfunction of endothelial cells are the microvascular alterations associated with diabetic neuropathy. Particular modifications consist of:

- Vascular tight junction-associated proteins have decreased.

- Thickening of the nerves' microvascular basement membrane
- Increased vascular endothelium proliferation and edema
- deterioration of pericytes

These alterations cause vascular constriction, which impairs blood flow and causes ischemia and hypoxia in the tissue of peripheral nerves. Schwann cells and neurons are harmed by the hypoxic neural microenvironment, which intensifies oxidative stress and inflammation.[26,27]

Recent studies indicate that nerve ischemia is caused by decreased microvascular permeability rather than general changes in blood volume. According to the theory of capillary temporal heterogeneity (CTH), high CTH impairs neurological function by causing inefficient oxygen extraction, endothelial dysfunction, and low tissue oxygen tension.[28]

The question of whether microvascular alterations cause or contribute to the development of diabetic neuropathy is still up for dispute. Certain studies indicate that through modified endothelial barriers and neurogenic processes, diabetic neuropathy itself may contribute to microvascular diseases.[29,30]

In summary, microvascular changes appear to play a major role in nerve injury through lower blood flow, oxygen delivery, increased oxidative stress, and inflammation in nerve tissue; however, the precise significance and timing of these changes in diabetic neuropathy remain unclear.

Role of inflammation

The process by which inflammation caused by diabetic neuropathy results in damage to nerves is confusing. Studies on humans have not found much evidence of normal inflammatory neuropathy; nonetheless, diabetes in animals has been shown to cause temporary elevations in spinal microglia and peripheral nerve macrophages. Rather than widespread inflammatory infiltrates, the main characteristic seems to be a dysregulation of the neuroinflammatory system. Different mechanisms play a significant role.

Chemokine signaling

Diabetic neuropathy is characterized by increased chemokine/receptor signaling. Important pathways are CXCL12/CXCR4, CXCL13/CXCR5, and CCL1/CXCR8. Inflammatory cells

are drawn in and pain signals are amplified in the nervous system as a result of this enhanced signaling.[31]

Cytokine dysregulation

Proinflammatory cytokines such as TNFα, IL-1β, IL-6, and interferon-γ are significantly elevated in diabetic neuropathy. These cytokines are involved in both pain sensitivity and tissue destruction. The expression of different inflammatory mediators is influenced by modifications in transcription regulators such as Nrf2 and NF-κB, which further regulate the inflammatory response.[32]

Bradykinin receptor upregulation

Bradykinin B1 and B2 receptor expression is upregulated in the spinal cord of patients with diabetic neuropathy. This overexpression increases sensitivity to pain and fuels neuroinflammation. In animal studies, neuropathic pain may be lessened by antagonists to these receptors.[33]

Enzyme induction

A key factor in diabetic neuropathy is the activation of enzymes including cyclooxygenase-2 (COX-2) and isoforms of nitric oxide synthase. These enzymes contribute to both neuropathic pain and degenerative neuropathy by inducing ischemia hypoxia and oxidative/nitrosative stress.[34]

Glial cell activation

Although there are no widespread inflammatory infiltrates, neuroinflammation is greatly influenced by the activation of glial cells, specifically microglia in the spinal cord and Schwann cells in peripheral nerves. Inducing changes in pain signaling and nerve function, these stimulated cells release neurotrophic substances such as BDNF and proinflammatory mediators.[35] Together, these many inflammatory pathways have a role in the onset and advancement of diabetic neuropathy leading to severe nerve damage.

Impaired neurotrophic support

Through the involvement of nerve growth factor (NGF), the study sheds light on a critical mechanism in the development of diabetic peripheral neuropathy (DPN). Researchers discovered a substantial correlation between lower serum NGF levels and the occurrence of DPN. Higher HbA1c levels, a longer duration of the disease, and other clinical indicators of

more severe diabetes were all connected with this decrease in NGF. Neuronal growth, survival, and function are all critically dependent on NGF, and neuronal death and dysfunction in diabetes conditions seem to be greatly exacerbated by NGF's reduction. The study indicates that one of the key pathways causing nerve damage in diabetic neuropathy is decreased NGF signaling.[36,37]

Altered ion channel function

Ion channel function is significantly altered in diabetic neuropathy, with voltage-gated sodium channels (VGSCs) being impacted most. VGSCs are upregulated in diabetes circumstances, particularly Nav 1.7 and Nav 1.8, which are important for nociceptive perception. In diabetic individuals, this elevated expression has a role in neuropathic pain and hyperalgesia. Furthermore, sorbitol accumulation-induced decreased Na+/K+ ATPase activity causes a modest depolarization of nerve cells, which heightens their susceptibility to stimuli. In conclusion, a key factor in the development of diabetic neuropathy is altered expression and function of ion channels, especially sodium channels. Knowing these pathways helps to create targeted medicines to treat diabetes patients' neuropathic pain; one promising route for future interventions is to focus on specific sodium channel blockers.[38,39] The aforementioned pathways ultimately result in peripheral neuropathy, which damages the nerves in the foot, by interplaying with sensory-motor impairments, axonal degeneration, demyelination, and autonomic dysfunction. All of these processes weaken nerve signal transmission, affect mobility and sensation, and interfere with essential processes like the regulation of blood flow in the feet. Ultimately, this leads to a complicated neuropathic disorder that compromises general nerve activity in the limbs and adversely impacts foot health by making the feet more susceptible to infections, accidents, and ulcers.[40]

Injury and Ulcer formation

Studies have identified several risk factors associated with diabetic foot ulcers. These factors encompass patient demographics like male gender, advanced age with diabetes (over 10 years), and higher body mass index. Diabetic complications including retinopathy, peripheral neuropathy (particularly sensorimotor and autonomic types), peripheral vascular disease, and uncontrolled blood sugar (HbA1c) also significantly elevate risk. Additionally, foot health plays a crucial role. Deformities, high plantar pressure, infections, and inadequate self-care practices all contribute to ulcer development.[41,42] Notably, peripheral neuropathy is a critical factor, potentially leading to high pressure areas, deformities, and imbalances – all of which

substantially increase the risk of ulceration.[43] Furthermore, foot deformities and gait instability can exacerbate plantar pressure, creating a potentially cyclical process. This highlights the necessity of comprehensive diabetic care, encompassing foot care education and meticulous management of neuropathy and other identified risk factors.[44]

The growing global epidemic of diabetes, particularly the rise of type 2 diabetes, has driven increased focus on diabetic foot disease.[45] With a lifetime risk of foot ulcers as high as 25% and amputations occurring every 30 seconds worldwide, the burden of this complication is significant. The presence of peripheral neuropathy and vascular disease in over 10% of newly diagnosed type 2 diabetics, coupled with a particularly high risk for ulcers and amputations in the first year after diagnosis, paints a concerning picture.[46] This risk is further amplified in developing nations, where diabetes prevalence is expected to surge and neuropathic ulcers, more preventable than ischemic ones, are more common. India, with the highest diabetic population globally, exemplifies this challenge, experiencing frequent foot complications and amputations often linked to delayed presentation, neuropathy, and infection. Cultural factors further complicate matters, as barefoot walking and reliance on traditional healers can delay proper medical intervention.[47,48]

Different mechanism involved in ulcer formation are

Loss of protective sensation

Loss of sensation in the feet increases the risk of unnoticed injuries. Patients may not detect minor cuts, blisters, or pressure sores, which can progress to ulcers. Diabetic neuropathy significantly compromises foot health.[49] It damages sensory nerves, reducing the ability to feel injuries. Motor nerve damage increases pressure on the soles, further damaging tissues. Autonomic neuropathy disrupts sweat production, temperature regulation, and skin integrity. These factors combine to impair blood flow, increase infection risk, and promote ulcer formation. High blood sugar can damage nerves responsible for feeling your feet. This "numbness" can mask injuries like cuts, blisters, or even burns, allowing them to go unnoticed and worsen. This emphasizes the critical need for meticulous foot care in diabetic individuals to prevent such complications.[50,51]

Impaired Healing and Oxidative stress state

While low levels of reactive oxygen species (ROS) play a beneficial role in wound healing, particularly in fighting external damage, excessive ROS production creates a major problem in diabetic wounds.[52] This imbalance, known as redox imbalance, is caused by high blood

sugar (hyperglycaemia) and low oxygen levels (tissue hypoxia) in diabetic wounds. Studies have linked this highly oxidizing environment to delayed wound repair. Furthermore, long-term type 2 diabetes significantly reduces the body's natural antioxidant defences, further exacerbating the problem. This oxidative stress is believed to hinder diabetic wound healing through various mechanisms, including direct skin injury, nerve damage (neuropathy), insufficient blood flow (ischemic lesions), and increased susceptibility to topical infections.[53-54] During the injury, inflammatory cells like neutrophils and macrophages release ROS as a part of the immune response. In diabetic patients, this ROS production is surged due to existing oxidative stress, further damaging tissues.[52]

Hyperglycaemia, a hallmark of diabetes, is a well-established trigger for oxidative stress. This excessive production of free radicals has a detrimental impact on the peripheral nervous system. It disrupts blood flow, nerve structure, and metabolism, leading to widespread damage throughout the system. Schwann cells, myelinated axons, and sensory neurons in the dorsal root ganglia are all negatively affected.[55] Furthermore, insufficient ATP (energy) production due to mitochondrial dysfunction in axons hinders their ability to transport essential materials. This combination of oxidative stress and energy depletion ultimately leads to axonal injury and death (degeneration or apoptosis) through multiple biochemical pathways. These findings highlight the critical role of oxidative stress in the development of diabetic neuropathy.[56] In addition, Hyperglycaemia activates the hexosamine pathway, ultimately leading to increased production of TGF-β1 and PAI-1, both of which can hinder wound healing. Additionally, hyperglycaemia and NF-κB signaling induce the expression of thrombospondin 2 (TSP2), a protein involved in wound repair but potentially problematic in diabetic wounds. This combination of factors suggests a mechanism by which hyperglycaemia can impede the body's natural wound healing processes.[57,58]

Diabetic foot ulcer to cancer progression

Research since the 1990s suggests a link between diabetes mellitus (DM) and various cancers, including liver, breast, colon, endometrial, pancreatic, and kidney.[59] While potential mechanisms like hyperglycaemia, hyperinsulinism, inflammation, and oxidative stress have been identified, the exact nature of this association remains unclear. It's uncertain if DM directly causes cancer or if shared risk factors like obesity, aging, and inactivity are the primary culprit. Additionally, whether certain diabetic subgroups are more susceptible to

cancer requires further investigation. Studies on the duration and severity of hyperglycaemia may offer insights into this complex relationship.[60,61]

Pathophysiology

Chronic leg and foot ulcers are a growing concern for elderly populations, with increasing prevalence due to the aging demographic. These ulcers are primarily caused by three main conditions: chronic venous insufficiency (CVI), peripheral arterial disease (PAD), and diabetic neuropathy-induced ulcers.[62] Notably, inflammation appears to play a crucial role in the development of cancer within chronic wounds. This connection is supported by studies demonstrating a slight but statistically significant decrease in squamous cell carcinoma (SCC) risk among individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin or ibuprofen.[63]

Wound healing and epithelial cancer progression share surprisingly similar physiological pathways. During re-epithelialization, a key phase of wound healing, keratinocytes undergo hyperproliferation and migration to close the wound. This bears a strong resemblance to the uncontrolled proliferation and migration seen in cancer initiation and metastasis. The critical difference lies in the self-limiting nature of wound healing – once the wound is closed, these hyperproliferative behaviors cease. Several factors contribute to this intricate process: the epidermal growth factor (EGF) family that regulates cell growth and movement, along with other cytokines like fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and hepatocyte growth factor (HGF).[64] Matrix metalloproteinases (MMPs) further complicate the picture, as their uncontrolled expression hinders wound healing while promoting metastasis. The link between chronic wounds and cancer development has been a topic of discussion for a century. Potential reasons include the imbalanced cytokine profile within the wound environment, mutagenic effects from necrotic tissue toxins, and a decline in immune cell activity (particularly dendritic cells) within scar tissue. This compromised immune response allows malignant cells to evade detection and become more aggressive and metastatic. The exact cause, however, remains elusive, likely a complex interplay of environmental, immunological, and genetic factors.[65,66]

Attributes of marjolin's ulcer

Marjolin's ulcer (MU), a rare but aggressive form of skin cancer, arises in areas of pre-existing damage or chronic inflammation.[67] Burn scars hold the highest risk (1-2%), but MU can also develop in other scar tissues and chronic wounds. Men are more susceptible than

women, with a peak incidence in the fifth decade of life. The risk of malignancy is highest in burn scars (76.5%) and decreases significantly in chronic wounds from trauma (8.1%), venous insufficiency (6.3%), and osteomyelitis (2.6%).[68,69] Interestingly, while pressure ulcers rarely transform into MU (0.5%), some argue these ulcers may have a more aggressive course. Time of onset can categorize MU as acute (within 1 year) or chronic. The reported timeframe for malignant transformation varies widely, from 4 weeks to 75 years.[70] Patients with compromised immune systems are more susceptible. Several signs suggest malignant transformation in a chronic wound: nodules, hardened tissue, irregular edges, excessive granulation tissue, growth over time, bleeding, and lack of healing within 3 months. Due to potential diabetic neuropathy-induced painlessness, a biopsy is crucial for diagnosis.[71]

Squamous cell carcinoma in chronic ulcers

Squamous cell carcinoma (SCC) is the most common cancerous tumor found in scars and chronic wounds, making it the leading carcinoma in these areas. Generally, SCC is the second most frequent skin cancer. Arising from keratinocytes in the epidermis, SCC is characterized by invasive growth and a tendency to spread to nearby lymph nodes. SCC developing in chronic wounds or scars is considered more aggressive than SCC from other origins and carries a higher risk of metastasis and recurrence if left untreated. Early signs often appear as a small, scaly bump or plaque that progresses into a hard, protruding lesion. In some cases (32% of malignant ulcerations), the SCC may present as a more diffuse process at diagnosis.[72,73] Once SCC is confirmed, checking for metastasis is crucial, particularly in lower extremity SCC which has a metastasis rate around 27-30%. Larger tumors, blurred margins, rapid growth, ulceration, poor differentiation, deep invasion into fat layers, and infiltration around the wound or blood vessels are all considered high-risk characteristics for SCC. The risk of metastasis is also higher in recurrent SCCs. Distant metastases typically target the brain, liver, lungs, kidneys, and distant lymph nodes. Metastasis is the most significant prognostic factor, with affected lymph nodes reducing life expectancy to 2-3 years.[74,75]

Clinical manifestations

Tissue samples should always be obtained if a Marjolin's ulcer is suspected in order to confirm or rule out the diagnosis. It is important to develop standardised biopsy protocols in order to boost the accuracy of cancer diagnosis rates. It is important to collect tissue samples from different areas of the ulcer and its border, and the examiner should have experience

evaluating skin samples.[67] Thus, the number of erroneous negative outcomes can be reduced. Following diagnosis confirmation, x-rays of the affected extremity and ultrasound evaluation of the anatomical lymphatic drainage region are required to evaluate the disease's local and distant extent. Diffuse demineralization and destruction on x-rays are indicative of osteomyelitis, which is typically the result of bone involvement. Estimating the amount of bone involved in pressure ulcers in the sacral or iliac regions may be far more challenging. In certain places, computer tomography (CT) can provide further information. When it comes to SCC, magnetic resonance imaging (MRI) is thought to be the most effective method when compared to computed tomography (CT) for determining the degree and course of bone loss as well as soft tissue inflammation. SCC and metastatic lesions are hypointense on T1-weighted sequences.[76,77]

Management of diabetic foot ulcer

Blood glucose control

Patients with diabetic foot ulcers benefit significantly from long-term management of their blood sugar levels. Self-monitoring of blood glucose, a cornerstone of diabetes care, empowers patients to track their sugar levels throughout the day. The frequency of these measurements should be personalized to each patient's specific needs and treatment goals. To optimize treatment plans, healthcare teams can combine blood sugar readings with dietary history, medication adjustments, exercise routines, and the use of glucose-lowering medications (both insulin and non-insulin therapies). Glycated haemoglobin (HbA1c) serves as the gold standard for evaluating long-term glycaemic control. Individualized HbA1c targets are crucial, and treatment goals should be established collaboratively with patients after considering various medical, social, and lifestyle factors. The overall aim is to achieve HbA1c levels as close to normal as possible without inducing significant hypoglycaemia. In most cases, target HbA1c should be below 7%, with pre-meal capillary plasma glucose levels between 4.4 and 7.2 mmol/L (80-130 mg/dL) and peak post-meal capillary plasma glucose levels below 10.0 mmol/L (180 mg/dL).[78]

Debridement/ Wound bed preparation

In chronic wounds, debridement, the meticulous removal of necrotic tissue, debris, and excessive bacterial colonization, serves as a cornerstone of successful treatment. This intervention creates a clean and optimal environment for healing, which would otherwise be impeded by the presence of devitalized tissue and a high bioburden.[79] Debridement offers a

multitude of benefits, including facilitating drainage, promoting granulation tissue formation, and reducing bacterial burden. It can be achieved through various techniques, each with its advantages. Surgical debridement, considered the gold standard, utilizes scalpels for swift and effective removal of dead tissue. However, meticulous technique is crucial to preserve healthy tissue. Enzymatic debridement offers a selective approach, employing enzymes to break down necrotic tissue without harming viable tissue. This method proves particularly beneficial for ischemic ulcers where surgical debridement is excessively painful.[80,81]

Antibacterial management

Due to the heightened risk of serious complications and death from infection in diabetic foot ulcers, even subtle signs warrant early and intensive treatment. This approach is more aggressive than that typically taken for wounds arising from other causes (with the exception of immunocompromised patients). It's important to note that the ideal duration of antibiotic therapy remains unclear and should be determined based on the infection's severity and the patient's response to treatment.[82]

Pressure offloading

In patients with peripheral neuropathy, offloading at-risk areas of the foot is crucial to prevent tissue damage and ulceration caused by uneven pressure distribution. This is especially important for promoting healing of existing plantar ulcers, as improper offloading significantly increases the risk of recurrence even after closure. The gold standard for offloading is a non-removable total contact cast (TCC), a well-molded cast that evenly distributes pressure across the entire foot's plantar surface. However, for patients with severe foot ischemia, deep abscesses, osteomyelitis, or poor skin quality, removable offloading devices like cast walkers, boots, or healing sandals are necessary alternatives. These patients may also require the use of crutches, walkers, or wheelchairs for mobility.[83,84]

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) utilizes a specialized pump (vacuum-assisted closure) to deliver continuous or intermittent sub-atmospheric pressure to the wound bed. This system employs a celled foam dressing connected to the pump via an adhesive drape, creating a closed environment. Wound exudates, bacteria, and pro-inflammatory cytokines are then drawn away from the wound and collected in a canister. By promoting blood flow, reducing tissue edema, and clearing the wound of these impediments, NPWT fosters an optimal environment for healing. Ideally, NPWT is implemented after debridement and

continued until healthy granulation tissue forms on the ulcer surface. While currently indicated for complex diabetic foot wounds, it is contraindicated for ulcers with active bleeding.[85]

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) offers a unique approach to wound healing for diabetic foot ulcers. In this therapy, patients breathe pure oxygen intermittently within a pressurized chamber. The pressure within the chamber is increased to 2-3 times that of sea level, while the patient receives 100% oxygen. These sessions typically last 1-2 hours and are repeated 30-40 times over the course of treatment. HBOT is particularly beneficial for patients with ischemic wounds, where poor blood flow hinders healing. By significantly increasing the amount of oxygen delivered to the wound site, HBOT can promote healing and potentially help avoid amputation.[86,87]

Reconstructive surgery

Diabetic foot ulcers with exposed bone, tendons, or minimal size reduction after two months of conservative treatment may require reconstructive surgery. This surgery aims to repair the damaged tissue and promote healing. The specific surgical approach depends on the available healthy tissue (donor site) and the size and depth of the ulcer. Surgeons may utilize skin grafts for simpler cases. For more complex wounds, various flap procedures are available, including local flaps (repositioning nearby healthy tissue), regional flaps (using tissue from the same leg), or even free flaps (tissue from another part of the body). Common flap options for foot ulcers include local transposition flaps, V-Y plantar flaps, and muscle flaps. Additionally, procedures to address underlying biomechanical issues, such as tendon tightness or claw toes, can be performed alongside reconstruction to prevent future ulcer formation. These corrective procedures can involve Achilles tendon lengthening or flexor tenotomies (cutting a tendon) to improve foot function and pressure distribution.[88,89]

Other novel therapies

Diabetic foot ulcer treatment is constantly evolving, with new therapies emerging alongside established methods. Bioengineered skin substitutes offer a promising addition to standard wound care for non-infected ulcers. These substitutes act as artificial skin, potentially aiding healing. Similarly, growth factors like PDGF-beta and platelet-rich plasma (PRP) may promote tissue regeneration. Extracellular matrix proteins and matrix metalloproteinase (MMP) modulators are also being explored for their ability to influence the wound healing

process. While some studies have shown encouraging results with these novel approaches, well-designed, randomized trials are necessary to definitively establish their role in treating diabetic foot ulcers.[90,91]

CONCLUSION

Diabetic neuropathy and its complication such as diabetic foot ulcers, present a significant challenge in diabetes management. The complicated interactions between inflammatory, vascular, and metabolic pathways in nerve injury highlight the necessity of an integrated approach for both prevention and treatment. For neuropathy to be prevented from developing into a malignant change, it is essential that the condition be identified early and treated aggressively. For the management of diabetic foot ulcers, the comprehensive approach is required such as wound care, offloading, glycemic control, antibacterial control and advanced therapies. Novel therapeutic approaches such as bioengineered skin substitutes, growth factors show the promising action but further studies are required to establish their efficacy. Although rare, the possibility of malignant change in chronic ulcers emphasizes the significance of close observation and timely biopsy of suspected lesions. Going forward, reducing the burden of diabetic foot problems and improving the quality of life for those affected will require a focus on individualized treatment regimens, patient education, and interdisciplinary care. Even though there are many alternatives available with current treatments, ranging from advanced medicines to standard wound care, there is still a significant need for ongoing research and innovation. Subsequent endeavours ought to concentrate on creating more accurate diagnostic instruments, investigating regenerative treatments, and utilizing technologies for ongoing observation and prompt action.

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