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Chapter

Insight of the Pathophysiology of Diabetic Foot Ulcer

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Abstract

The implications of prolonged hyperglycaemia in diabetic individuals include an increased incidence of foot ulcers. Prolonged hyperglycaemia creates a toxic environment in diabetes nerves, particularly at the foot. It also contributes to the hypoxic situation in this region. This disorder causes the nerves, particularly those in the foot, to die and become incapable of responding to sensation stimuli. However, the pathogenesis of diabetic foot ulcers is largely unknown. This chapter attempts to describe the aetiology of foot ulcers through peripheral neuropathy, vascular disease, trauma and infection and explore the evaluation and diagnostic criteria and the current therapy and management of diabetic foot ulcers.

Keywords: hyperglycaemia, diabetic foot ulcer, neuropathy, vascular disease, trauma and infection

1. Introduction

Diabetes patients experience diabetic foot ulcer (DFU) as a result of prolonged hyperglycaemia, and it is the most common reason for hospitalisation. It is also associated with severe morbidity and mortality and, if not recognised and treated promptly, can result in limb amputation [1]. It also had an influence on the financial burden placed on patients, their families, society and the government for the treatment and management of DFU [2]. The risk of a patient with diabetes developing a foot ulcer has been estimated to be 19–34%, and the incidence rates for ulcer recurrence remain high which is 40% within 1 year after healing and 65% within 5 years [3].

Hyperglycaemia stimulates enzymes such as aldose reductase and sorbitol dehydrogenase, resulting in the conversion of intracellular glucose to sorbitol and fructose. The accumulation of these converted glucose products reduces the synthesis of myoinositol in nerve cells that are essential for energy production [4]. The chemical change caused by glucose also resulted in the depletion of nicotinamide adenine dinucleotide phosphate (NADP), which is required for the detoxification of reactive oxygen species (ROS) and the synthesis of the vasodilator, nitric oxide (NO). As a result, there is an increase in oxidative stress on nerve cells, as well as an increase in vasoconstriction on blood vessel, which leads to ischemia, which causes nerve cell damage and death [5]. The common sites for ulceration on foot are dorsal or plantar aspects of the toes, plantar metatarsal heads and heel.
There are numerous events in diabetic progress that can contribute to the development of DFU. The most important events are diabetic peripheral neuropathy (DPN), which affects half of all diabetics, peripheral vascular disease (PVD) and trauma and infection [6].

1.1 Diabetic peripheral neuropathy (DPN)

DPN can be sensory, motor or autonomic. Sensory neuropathy reduces the patient's sensory awareness and manifests clinically as burning, tingling or paraesthesia in the stocking and glove distribution, which worsens after numbness symptoms appear [7]. The peripheral nerve fibres in diabetic patients are affected in a length-dependent manner, with the longest nerves being affected first, resulting in a stocking distribution of sensory loss. Sensory loss involving type A myelin fibres results in loss of proprioception, pressure sensation, vibratory perception and gait impairment. The destruction of type C sensory fibres results in an inability to recognise painful stimuli. As a result of these impaired sensations, the diabetic patient may suffer from repetitive foot trauma, such as blister formation or even metatarsal bone fracture, without realising it. Poor balance due to loss of proprioception, decreased sweating and dry skin that can develop skin cracks and fissures are all consequences of DPN [8].

Motor neuropathy can result in structural changes in the shape of the foot. It is typically presents as wasting of the intrinsic muscles of the foot, resulting in clawing of the toes and changes to the architecture of the mid-foot and subsequently in pressure redistribution over the metatarsal heads. Loss of the Achilles reflex is the earliest sign of these changes. With atrophy of the lumbricals and interosseous muscles, the anatomy of the foot arch changes, with a relative increase in extensor tendon forces producing a “claw” deformity of the toes. A shift to extrinsic muscle/tendon function contributes to depression of the metatarsal heads, hammer-toe contracture of the digits and equine ankle deformity [9].

Whereas autonomic neuropathy can impair the microvascular thermoregulation and anhidrosis process that adds to the motor and sensory disturbance. From this malfunction, the skin becomes dry as it loses the ability to moisturise its surface due to decreased secretory functions of the sebaceous and sweat glands and prone to fissuring, diminishes its effectiveness as a barrier to microorganism invasion, becoming susceptible to dermal infection, that is, cellulitis [10].

1.2 Peripheral vascular disease (PVD)

Microvascular and macrovascular diseases are the two types of diabetic vascular complications. Endothelial cellular dysfunction and smooth muscle abnormalities develop in diabetics as a result of a decrease in endothelium-derived vasodilators, resulting in constriction of blood arteries in the foot [11]. In diabetic patients, glucose levels in cells and tissues rise, stimulating glycolytic and polyol pathways in the peripheral nerve. Furthermore, protein modification with Advanced Glycation End-products (AGEs) and AGE accumulation causes structural (nerve fibre loss or demyelination and thickening of the endothelium's basement membrane in microvessel) and functional damage in small fibre nerves and microvessel. This situation is more vulnerable to diabetic patients’ distal lower limb microvessel, which typically affects small arteries below the knee and within the foot, resulting in ischaemia at this site. This microcirculatory complication appears much earlier in the stage of prediabetes and worsens over time [12].
Furthermore, macrovascular disease such as atherosclerosis causes blockage in major arteries due to thickening of blood capillaries and hardening of arteriolar walls, and it’s also ended up with ischaemia. In DFU, determining the degree of ischaemia is critical. The pedal pulses (dorsalis pedis and posterior tibial arteries) must be carefully palpated. The dorsalis pedis artery is absent or significantly reduced in size in approximately 12% of the population, so a pulse may not be palpable. A cool foot with no palpable pedal pulses should be investigated further with non-invasive arterial Doppler ultrasonography of the lower limb. Beside these, other risk factors can also contribute into PVD such as age, smoking, hypertension, hyperlipidaemia, inflammatory markers and renal dysfunction [13].

1.3 Trauma and infection

Trauma might also contribute to the development of ulceration in DFU. Ill-fitting shoes are the most prevalent source of trauma, and also injuries go missed due to a lack of sensation [14]. Motor neuropathy causes structural changes in the structure of the foot; as a result, many regular shoes are inappropriate for diabetic patients. Walking-related repetitive stress, along with diminished sensation and proprioception, predisposes to skin damage by producing atrophy and displacement of protective plantar fat pads, leading to ulceration and infection with inadequate skin protection or inappropriate footwear [15].

Neglecting skin protection, such as forgetting to apply moisturising lotions or failing to recognise cutaneous stress (redness, blister formation), can lead to ulceration.
and the development of an invasive soft-tissue infection. If not treated quickly, tissue degradation will persist, especially if the patient continues to walk. The risk of ulceration increases significantly in the presence of peripheral neuropathy, foot deformity or previous digit amputation (by 32 times) [1].

Trauma in the foot could also lead into infection that penetrates the deep fascia, allowing infection to spread into the mid-foot muscles, joints and tendon sheaths. In diabetics, infection is responsible for 50% of all major (above- or below-knee) lower-extremity amputations. Polymicrobial infections (staphylococci, streptococci, enterococci, Escherichia coli and other Gram-negative bacteria) are widespread, as is the presence of antibiotic-resistant bacterial strains, particularly methicillin-resistant Staphylococcus aureus, which occurs in 30–40% of cases. When a diabetic foot infection contains resistant bacterial strains, which is commonly the result of repeated or protracted antibiotic use, the risk of amputation rises [16]. The common pathway to DFU is illustrated in Figure 1.

2. Evaluation and diagnosis of DFU

Diabetic patients need to regularly check their foot from any sign of ulcer and infection. A typical foot examination encompasses four aspects which are dermatologic, vascular, neurologic and musculoskeletal.

2.1 Dermatologic

The dermatologist will look for any thickness or discoloration of the toenails, as well as hyperkeratosis on the toes or balls of the feet. The state of the patient’s skin reveals information regarding the health of the patient’s feet. Toenails that are excessively swollen, opaque, disintegrating, yellow in colour and malodorous are most likely fungal, indicating sensory, autonomic or both neuropathies. Peripheral neuropathy dulls the sensation and allows patients to bear more sustained pressure on a small region of skin without experiencing pain. Shear pressures induce the skin to react to aberrant stimuli, causing keratinisation to rise. Autonomic neuropathy makes it difficult to maintain normal skin moisture balance and control. The skin becomes either too dry and scaly or too wet, promoting dermatophyte infections and skin maceration inside the webspaces [9, 16, 17].

2.2 Vascular

Palpation of the dorsalis pedis and posterior tibial is part of the vascular examination. Because the dorsalis pedis artery is missing or diminished in size in the majority of diabetes individuals, a palpable pulse cannot be felt. The capillary refill time to each digit is also essential in determining blood flow to the toes and the microvasculature’s state. Peripheral oedema may be indicative of autonomic neuropathy caused by venous blood insufficiency in the lower extremities. The lower legs have dark discoloration up to the mid-tibia [18].

2.3 Neurologic

The neurologic evaluation involves testing the patellar and Achilles deep tendon reflexes. The loss of the Achilles reflex is a sign of severe peripheral neuropathy.
Sensitivity is assessed for vibratory loss using a 128 Hz tuning fork, while sensation to light touch is determined using microfilament, pin prick and temperature (tuning fork placed in warm or ice water then applied to dorsum of foot and positional sense in the toes). Neuropathy is characterised by decreased proprioception and a loss of light touch. Balance issues will be revealed by gait analysis. Walking from heel to toe might be challenging with peripheral neuropathy. A patient's larger base of gait may suggest lack of proprioception, and balance may be considerably reduced with the eyes closed. The Romberg test (loss of balance with feet together and eyes closed) is also used when evaluating neuropathy [19].

2.4 Musculoskeletal

The musculoskeletal assessment involves looking for common foot abnormalities such as bunions (hallux valgus), constricted toes and Tailor's bunions (lateral exostosis fifth metatarsal head). With the patient upright, clinicians should look for any noticeable asymmetry changes in arch height. Common symptoms of a patient's foot “looking odd” or changing in appearance and becoming red, hot and swollen without any history of trauma to the region should prompt a radiograph and referral to a podiatrist for treatment. Unexplained swelling in the feet is a sign of active Charcot alterations, especially if just one foot is affected. Diabetic foot infection, osteomyelitis and cellulitis, acute inflammatory arthropathy, gout, acute thrombosis and trauma are all causes of a Charcot deformity [20].

2.5 Imaging

In an acute presentation of a DFU, plain radiography is the most frequent first-line radiographic study to check for underlying osteomyelitis. It is cheap and widely available. If feasible, weighty viewpoints should be taken. Radiographs can identify osteomyelitis, osteolysis, fractures, dislocations, medial arterial calcification, soft tissue gas and foreign substances, as well as structural foot abnormalities and the presence of arthritis [20]. CT scans may be used to evaluate suspected bone and joint disease that is not visible on conventional radiography. CT provides excellent anatomic information and resolution of bone, including osseous fragmentation and joint subluxation. Subluxation of the transverse tarsal or tarsometatarsal joints can be seen prior to being visualised on radiographs [21]. Because of its enhanced resolution and ability to visualise the extent of any infectious process, MRI is usually preferred over CT for the investigation of osteomyelitis. MRI is frequently used in evaluating both soft tissue and bone pathology. This scan may be used to help diagnose osteomyelitis, deep abscesses, septic joints and tendon rupture. MRI is particularly sensitive for bone infection and may also be utilised for surgical planning [22].

3. Current therapy and management of DFU

The strategy for the management of patients with a DFU is a multidisciplinary approach to address the multifactorial processes involved in DFU. It includes all relevant specialties team such as nursing, orthopaedics, plastic surgery, vascular surgery, nutrition and endocrinology. This approach can decrease the risks DFU and amputation by 50–85%, lowering the cost medication and leading to a better quality of life for patients with DFU.
3.1 Treatments for diabetic peripheral neuropathy (DPN)

Pharmacological treatment is used to control the painful sensation of DPN which manifested as numbness, burning, stabbing or excruciating or intractable pain. The U.S. Food and Drug Administration (FDA) has approved three drugs for the pain associated with DPN, namely, pregabalin, tapentadol and duloxetine. Besides that, analgesics such as tramadol, acetaminophen and opioids such as oxycodone also have been prescribed for pain associated with DPN. However, these drugs produced many sides effect such as constipation and nausea and had high tendency to be misused. Antidepressants such as amitriptyline, nortriptyline and venlafaxine have shown and efficacy in DPN management, but the doses in clinical trial are not reproducible in clinical practice [22].

Antioxidants such as Alpha-lipoic acid (ALA) have been shown to be a possible treatment agent for DPN by delaying or reversing nerve damage [23]. Treatments based on mesenchymal stem cell (MSC) generated from adipose tissue might potentially be regarded as possible DPN treatments. These medicines increase the production of pro-angiogenic, neuroprotective and anti-inflammatory substances, which improves the clinical presentation of the illness [24]. Biological treatment with lower doses of IL-6 also can help increase blood flow, reduce chronic inflammation, repair peripheral nerve fibre and restore DPN peripheral nerve function [25].

3.2 Treatments for peripheral vascular disease (PVD).

In diabetic patients, a decrease in blood flow in both the microvascular (capillaries) and macrovascular (arteries and veins) systems, as well as a decrease in angiogenesis, raises the risk of ischemia. Tissue ischemia manifesting as dependent rubor with rest discomfort, ulceration or gangrene necessitates rapid examination for correctable artery occlusive disease in order to enhance perfusion and save limbs. In general, all patients with foot lesions and vascular testing revealing an ankle pressure of 100 mm Hg or toe pressure of 55 mm Hg should have arterial imaging investigations performed to identify occlusive lesions amenable to revascularisation such as open bypass or endovascular treatment [14]. In cases of common femoral artery occlusion, bypass is more successful and provides extended patency. Whereas, endovascular treatment similar to angioplasty in which a tiny balloon is inserted into a constricted portion of an artery and inflated to open the artery to enhance blood flow in the lower extremities [26]. Atherectomy is another method that uses a spinning cutting blade to remove atheroma. Diabetic patients must get multidisciplinary care, including medication for hypertension, hypercholesterolemia and bleeding, in order for these procedures to be effective [27].

3.3 Relief of foot pressure

The persistent and recurrent traumatism of the foot, as well as the use of inappropriate footwear, contributes to the development of a DFU. Both lower extremities should be inspected for skin trauma (redness, induration, oedema), ulceration, foot/toe deformity and popliteal and ankle (posterior tibial, dorsalis pedis) pulses palpated. The education on precise foot care and suitable footwear must be stressed in the diabetic patient. Diabetic patients should be taught to self-examine their skin and feet on a regular basis, as well as be educated on skin care and footwear management [28].
3.4 Infection treatment

Antibiotic treatment for DFU will be administered based on the pathogen that is most likely causing the infection and the severity of the illness. It can be tweaked based on the findings of the microbiological culture and the treatment's effectiveness. The duration of antibiotic treatment is determined by the severity of the illness; for example, a moderate infection might be treated for 1–2 weeks, a severe infection for 2–4 weeks and osteomyelitis for longer [29]. Dicloxacillin, cephalixin, clindamycin and amoxicillin/clavulanate are recommended antibiotics for mild-moderate cases; vancomycin + ampicillin/sulbactam, moxifloxacin, cefoxitin or cefotetan for moderate cases; and vancomycin + piperacillin/tazobactam, imipenem/cilastatin, meropenem or doripenem for severe cases [29, 30, 31].

3.5 Tissue engineering approaches

Tissue engineering is a regenerative medicine discipline that combines growth factors, cells and scaffolds to restore, preserve or improve damaged tissues or whole organs [32]. Growth factors are proteins that promote and activate cell proliferation by stimulating angiogenesis and the transcription of certain genes. Growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor beta (TGF) and vascular endothelial growth factor (VEGF) are examples of growth factors. All of these growth factors have been shown to be beneficial in DFU tissue healing [33]. Cells obtained from bone marrow and umbilical cord blood such as mesenchymal stem cells (MSCs), fibroblasts and keratinocytes have also been employed for tissue repair in DFU [33, 34, 35]. Furthermore, biomaterials derived from natural resources such as collagen, hyaluronic acid, fibrin, chitosan and alginate, as well as synthetic materials such as poly (acrylic acid) (PAA), polyglycolic acid (PGA), PCL-poly (ethylene glycol) (PEG), gelatin methacrylate (GelMA) have been used as hydrogels, bandages, foam and films in DFU treatment. These biomaterials have been recommended for used in DFU treatment because of their ease of degradation, good biocompatibility and resistance to the scaffolding material [36].

4. Conclusions

DFU frequently results in complications such as infection, osteomyelitis, abscesses and amputations of the lower extremities. It also has a significant influence on patients’ physical, psychological, social and economic elements, as well as their overall quality of life. The pathophysiology of DFU, on the other hand, is still unknown. It is critical to understand the pathophysiology of DFU in order to properly treat and manage the condition. Several causes, including diabetic peripheral neuropathy (DPN), which affects 50% of all diabetics, peripheral vascular disease (PVD) and trauma and infection, have been identified as critical events for DFU to develop. Many biological therapeutic remedies have been produced as a result of technical advances to help in the healing process of DFU. Tissue engineering is a revolutionary therapy for DFU that has the potential to lead to new treatments in the future.
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