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Introductory Chapter: Diabetic Foot

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1. Introduction

Diabetic foot disease is an important problem confronting the diabetologist, internists, and surgeons as it reduces patient's quality of life and affects social participation. It is including several chronic complications as infection, foot ulceration and even tissue destruction of the foot. These complications are considered as a significant cause of morbidity and mortality among diabetic patients. Consequently, chronic complications or diabetic foot disease are a growing concern worldwide and represent a major global medical, social, and economic problem.

Diabetic Foot Ulcer (DFU) is one of the most distressing complications and it is defined as the commonest major end-point of diabetic foot disease.

The main etiological factors for DFU are peripheral nerves damage and peripheral vascular disease. Series of mechanisms are documented such as decreased peripheral blood flow and decreased local angiogenesis.

Furthermore, biomechanical abnormalities and increased susceptibility for infection are associated factors exposing to DFU [1, 2].

2. Etiopathogenesis

The etiopathogenesis of diabetic foot disease is multifactorial with major factors. Neuropathy, microvascular disease and infection are mainly included. These factors are leading to foot tissue necrosis and ulcer occurrence [2, 3].

2.1 Neuropathy in diabetic foot

About 50% of patients with diabetes mellitus develop symptomatic peripheral neuropathy within 25 years of disease onset. Distal polyneuropathy is commonly encountered. Whereas combined neuropathies with motor and autonomic fibers involvement can occur. Age, disease duration and poor glyceamic control quality over several years are strong predictors, leading to diabetic neuropathy [4].

Hyperglycemia, dyslipidemia, insulin resistance and oxidative stress can contribute to diabetic neuropathy [5].

According to Rochester Study [6], the severity of the neuropathy is related to the duration of hyperglycemia exposure. Other factors are studied in current researchs focusing on oxidative stress, advanced glycation-end products, protein kinase C and the polyol pathway [7].

2.2 Vasculopathy

Peripheral vascular disease is among the main etiological factors in foot ulceration. Chronic hyperglycemia causes peripheral arteries damage, smooth cell abnormalities and endothelial cell dysfunction.

Endothelial dysfunction, owing to changes in the proliferation of endothelial cells, thickening of the basement membrane, leads essentially to microvascular disease which is responsible for ischemia. Hyperglycemia is also associated with an increase in thromboxane A₂ leading to plasma hypercoagulability [8].

2.3 Immunopathy

The immune system is compromised with hyperglycemia and research indicates the impairment of the immune system with serum glucose levels exceeding to 150 ml/dl. Thus, high blood glucose levels lead to inappropriate inflammatory response and disruption of cellular immunity (inhibition of fibroblast proliferation and impairment of the basal layer of keratinocytes, reducing epidermal cell migration) [8].

Consequently, diabetic patients are more exposed to the foot infection which is a limb-threatening and debilitating condition mainly seen in uncontrolled diabetes. The soft tissue infection adversely affects diabetic control. This repetitive cycle leads to uncontrolled hyperglycemia, further affecting the immune response to infection [9]. The bone can be involved in case of infection resistance responsible for soft tissue infection dissemination making osteitis.

Bad glycemia control associated with an open wound creates a catabolic state and a metabolic dysfunction affecting the synthesis of proteins, collagen and fibroblasts. Furthermore, systemic deficiencies are propagated leading to nutritional compromise in diabetes [10].

3. Classification

Many classifications of the diabetic foot are reported. The most commonly used is Wagner's classification, consisting of six simplistic wound grades used to assess ulcer depth (grades 0–5) [11]. This classification is limited as it is not able to recognize ischaemia and infection as independent risk factors in all classification grades [12]. A more recently proposed and popularized DFU classification is the University of Texas Wound Classification [13].

4. Clinical presentation

Clinical foot examination at each follow-up is important to detect the disease early such as ulceration or gangrene. The clinical examination includes inspection of the skin integrity, foot deformities such as, Charcot's foot, hallux valgus, claw toe, hollow foot, skew or flat foot. The muscular condition and the bone structure should be evaluated as well [4].

Hyperkeratosis with dry and fissured skin are features of polyneuropathy. Lower extremity vascular insufficiency is made by one or more signs of claudication, night or rest pain, atrophic integument, absent peripheral pulses and loss of limb hair [8].

About 50% of patients with DFU present clinical signs of infection which is clinically featured by the presence of purulent secretions or at least two of the inflammatory classic signs (painful swelling, edema, hyperemia). The lack of the

sensitivity in patients with impaired immune response due to neuropathy can make these signs masked [8].

5. Investigations

Guideline development group selected recommendations from the National Institute of Clinical Excellence. In their most recent publication, the annual assessment of the diabetic foot requires recommendations aiming essentially to assess both of peripheral neuropathy and peripheral vascular status.

Peripheral vascular disease is diagnosed by angiography which studies the peripheral arterial tree. Non-invasive vascular screening is currently more used in the diabetic foot to detect early the peripheral ischemia [14].

These investigations consist of Doppler ultrasound (for estimation of ankle brachial ratio), photo-plethysmography, transcutaneous oximetry, laser Doppler flowmetry and television microscopy [2].

Most guidelines recommend the use of Neurological foot testing with 10 g monofilament in order to assess diabetic neuropathy. An inability to sense a 10 g pressure is the current consensus definition of loss of protective sensation [15].

6. Management

The management of the diabetic foot complications is multidisciplinary and requires the collaboration of a specialist team comprising a diabetologist, surgeons, podiatrist, microbiologist, tissue viability nurse with a thorough understanding of foot function.

The aim is to decrease the risk of the disease progression leading to feet deformities, ulcers and foot amputation. The prognosis is mainly highlighted by factors such as glycaemic and blood pressure control, diabetic nephropathy and diabetic retinopathy [16].

6.1 Conservative therapeutic modalities

6.1.1 Glycemic control

It is demonstrating that a good controlled glycaemia delays the onset and slows the progression of diabetic neuropathy, retinopathy and nephropathy in patients with insulin-dependent diabetes mellitus [17, 18].

Callaghan et al. [12] showed the decrease in the risk of developing clinical neuropathy with better glycaemic control, in diabetes requiring insulinotherapy.

6.1.2 Pharmacological therapy

The medication adherence to oral diabetic drugs is improved by the patient education. The pain resulting from the distal neuropathy requires the use of pain killers. The National Institute of Clinical Excellence recommends use of first-line agent duloxetine and pregabalin for pain control [19].

Various risk factors for atherosclerosis mainly smoking, should be completely stopped in diabetic patients in order to decrease the risk of distal vascular disease. Adding to that the use of statins and antiplatelet medications reduce the limb ischemia risk and the vascularisation, when it is improved, it is in turn associated with a reduced amputation rate.

A targeted antibiotherapy based on the wound culture results is needed in DFU with superadded infection. The duration of treatment depends on the underlying infection severity [20].

6.1.3 Debridement

A 10-year review on standardized wound care protocol and integrated multi-disciplinary team showed a reduction in amputation rate in diabetic foot patients as they had not delayed debridement [21].

Disease activity is measured by the degree of swelling, erythema and especially skin temperature. Superficial ulcer requires the removal of necrotic and hyperkeratotic tissue as it promotes better the wound healing. Whereas, Deep wounds with bone and soft tissue involvement need more aggressive debridement with some involving surgery [20].

6.1.4 Foot pressure relief

The most important therapeutic principle is typically based on a quick and consistent pressure relief to promote wound healing as the weight bearing force is removed from the site of ulcer. The force redistribution is ensured by means of temporary immobilization, wearing of a protective cast or orthosis [22].

6.1.5 Wound dressings

A variety of dressing modalities are available with the advancement in the promotion of wound healing.

Dressing materials can be of various categories including natural, modified and synthetic polymers, as well as their mixtures or combinations, processed in the



Figure 1. *Wet gangrene of the toe with osteitis. Complete healing under antibiotic treatment and MMP's inhibitor (pharysor).*

form of films, foams, hydrogels and hydrocolloids. Furthermore, wound dressings can be used as medicated systems, through the delivery of healing enhancers and therapeutic substances (growth factors, peptides, drugs, stem cells and/or other bioactive substances) [2].

Randomized controlled trials [23], showed that Silver-impregnated dressings have not been shown to be more efficient in treating DFU.

Furthermore, “Moist dressings” are suggested to be more efficient than “dry dressings.” [24].

According to our experience in the “Olivier Private Clinic”, Sousse, Tunisia.

We noted the efficiency of Matrix Metalloproteinases (MMPs) inhibitors of natural or synthetic origin in the healing process of chronic diabetic wounds. We use mainly moist dressings with **Pharysor***, a MMPs inhibitor of natural origin, in diabetes with superficial and even with deep chronic ulcers. This agent has been found to be beneficial in improving wound healing rates (**Figures 1–4**).

Adding to that, our standard non-surgical management for DFU requires negative pressure wound therapy, close glycemic control and nutritional support with enriched oral nutritional supplement. A targeted antibiotherapy is further delivered in infected ulcers.



Figure 2.
Wet gangrene of the second toe with osteo-arthritis. Complete healing under antibiotic treatment and MMP's inhibitor (pharysor).



Figure 3.
Wet gangrene of the forefoot complete healing under antibiotic treatment and MMP's inhibitor (pharysor).



Figure 4. *Gangrene with osteitis of the calcaneus complete healing under antibiotic treatment, excision and MMP's inhibitor (pharysor).*

6.2 Surgical management of DFU

Surgeons interfere in the second line and surgical approach becomes necessary when conservative and medical alternatives are not sufficient. All reconstructive surgery techniques, in particular local flaps and skin grafts, can be used depending on the location and size of the substance loss.

Furthermore, possibilities of revascularization of the lower limbs are needed to improve the chances of skin healing in case of limb ischemia.

The therapeutic decision of partial leg amputation is not systematic and should be taken as a last therapeutic option. Amputation is typically recommended for deep and chronic non healing ulcers with necrotic tissues.

7. Prevention

Preventive strategies are important to decrease the risk of repeated ulcers and amputation. Measures are mainly based on patient education and foot assessments for peripheral vascular disease and neuropathy. Furthermore, foot pressure relief with individualized orthopedic shoe provision and insole treatment is necessary in order to adapt the pressure distribution to each foot. Consequently, lesions and chronic foot ulcers may be better prevented.

8. Conclusion

Diabetic foot is a chronic complication which poses challenges in the early diagnosis and management. Paying attention to this complication is necessary during the follow-up of diabetes. The treatment is often conservative with a proper glycemic control. Management of risk factors including peripheral vascular disease, neuropathy and infection is essential to avoid serious complications leading to amputation.

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