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The Pathogenesis of the Diabetic Foot Ulcer: Prevention and Management

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1. Introduction

The most important complications of diabetes mellitus are neuropathy and diabetic foot. Manifestations of resulting complications range from simple to highly complex, including limb amputations and life-threatening infections. Foot infections in people with diabetes are common; this creates complex social problems owing to the financial burden resulting from the high cost of treatment and healing (Aguilar, 2009). In addition to severe morbidity, foot infections cause prolonged hospitalization and psychological and social problems for the patient and his family. Even though foot pathology in diabetic patients entails high medical costs, it also causes loss of productivity in patients (Ramsey et al, 1999).

Predictions regarding the prevalence of DM have failed because the expected 300 million people worldwide with diabetes in 2025 were exceeded in 2011, some authors figure the rising to 347 millions (Goodarz et al, 2011), but in Lisbon, Portugal the International Diabetes Federation (IDF) said that the prevalence of DM around the world is 366 millions (Mbanya JC, 2011). Moreover, it is predicted that within 15 years (2025) there will be 500 million people worldwide with diabetes if we do not take the necessary measures to prevent the spread of this disease. On the other hand, the most common cause of non-traumatic amputations is diabetes mellitus, and 80% of these could be averted through adequate prevention and early intervention. For example, in 2002 the medical cost for treating patients with DM was 92 billion USD. Loss of productivity could represent an additional 40 billion. Projections for the cost of treatment will rise to approximately 160 billion in 2010 and close to 200 billion in 2020, or even higher (Hogan P et al, 2003). Therefore, complications arising from diabetic foot represent an important medical challenge in growing proportions. The cost of treatment of ulcerations without surgical interventions approaches several thousand dollars, and in some cases even more, compared to ulcers that are treated through amputation (Kruse & Edelman 2006). Foot ulcerations represent 85% of all amputations. Hence, the association between ulcers and lower extremity amputations is patently obvious. Taking into account that the major risk factor leading to amputation is ulceration, around 15% of all foot ulcers will ultimately require amputation at some point. Other risk factors for amputation include a long history of diabetes, peripheral neuropathy and structural changes of the foot, peripheral vascular disease, poor glycemic control, a prior history of foot ulcers,
previous foot surgery and/or amputation, retinopathy and nephropathy. (Clayton et al, 2009, Aguilar & Rayo 2000)

The management of wounds requires meticulous care and early treatment by a multidisciplinary foot care team. This management team may include: infectious disease specialists, microbiologists, podiatrists, nurses specializing in diabetes and physicians with knowledge of DM, all striving to provide quality care and good metabolic control. Optimal care and early detection of diabetic ulcers can greatly reduce the occurrence of infections. We think that all specialists who treat diabetic foot need to remember this important message: “Neuropathic symptoms correlated poorly with sensory loss, and the absence of sensory loss must not be equated to no risk of foot ulcers. Therefore, the assessment of foot ulcer risk MUST ALWAYS include a careful foot examination, with the removal of shoes and socks, regardless of the patient’s neuropathic history.” (Boulton et al, 1998).

Unfortunately, diabetic foot ulcers (infected or not), are quite often treated improperly. Amputation rates have shown a variation of both gender and ethnicity. Males are at higher risk than females. Hispanics -particularly Mexicans- and African-Americans have been associated with higher risk of amputation (Velasco Mondragon et al, 2010). Difficulty of access to continuing medical education for physicians, especially in emerging countries exhibiting high prevalence, has caused many difficulties in providing early care for patients and in establishing preventive care routines. Another worrisome matter is the propagation of erroneous beliefs regarding treatment of DM (for example, insulin being linked to blindness) and wound healing (for example the inappropriate use of honey, spider webs, gelatin, herbal preparations, etc. as cures) and also poor involvement of the Federal Government in health programs. These factors all lead to a rise in the disease, and consequently increased risk of amputation (Tentolouris 2010). Many scientific studies have led to the establishment of programs designed to prevent and promote awareness on diabetic foot complications. As a result, the rate of amputations dropped by nearly 50% (Li R et al, 2010).

The underlying causes of risk factors leading to the onset of diabetic foot ulcers have recently been identified. The afore-mentioned conditions, together with peripheral neuropathy, contribute to a lack of sensation in poorly vascularized lower extremities that are prone to the development of chronic wounds. Lack of sensation leads to exacerbation of the injury. Dry, stiff skin cracks easily and causes splits or fissures. A fissure in the protective epidermal covering (stratum corneum), can become infected, resulting in localized cellulitis or even small longitudinal ulcerations that can potentially become infected and frequently lead to the spread of infection and the ultimate loss of the lower limb, either partial or full. Poor circulation occurs in conducting vessels, consequently affecting microcirculation, which in turn affects the basement membrane, thickening and diminishing vascular reparative capacity (Tanenberg RJ & Donofrio PD 2008). The most important risk factors for the development of diabetic foot ulcers are: peripheral neuropathy (motor, sensory and autonomic), structural and anatomical deformities, environmental factors, peripheral vascular disease, a compromised immune system and poor metabolic control, in addition to social influences such as emotional, psychological and behavioral problems (Lyons 2008).

The purpose of this chapter is to help gain an understanding of different types of management strategies, ranging from general through specific strategies, starting with the initial examination of the patient who comes in for examination of a foot injury all the way through the final diagnosis. The clinical exam begins with a complete examination,
classification of the ulcer, basic measures, treatment with antibiotics (if the wound is infected) in order to establish the appropriate intervention and follow-up treatment to avert major complications, including amputation.

We hope that better insight of the pathogenesis of diabetic foot complications will contribute to creating improved, effective and successful preventive strategies in order to save lower limbs.

2. Pathogenesis of the wounds

Risk factors for the development of foot ulcers in diabetic patients should be evaluated from 3 different dimensions:

1. Physiopathology
2. Anatomical and structural alterations
3. Environmental influences

2.1 Physiopathology

These changes occur at a biomolecular level and are caused by hyperglycemia, which leads to the development of neuropathy, as described in Fig 1.

Over the past two decades considerable evidence has been accumulated to support the potentially pathogenetic role of a number of mechanisms that lead diabetic persons to develop wounds. The major mechanisms are: (Aguilar F, 2009a)

- Nerve hypoxia/ischemia
- Auto oxidative stress
- Polyol pathway overactivity
- Increased advanced glycation end-products
- Deficiency of gamma linolenic acid
- Protein kinase C, especially B-isoform increase
- Cytokines dysfunction
- Disorders of collagen molecules (elastin, proteoglycans)
- Endothelial dysfunction
- Mitochondrial dysfunction
- Growth factors deficiency
- Alteration of the immune mechanism
- Increased secretion of proteases
- Others

Under normal circumstances, wound repair is a highly orchestrated event that involves the interaction of the elements described above. Each stage of the healing process entails this orchestrated effort. The damaged tissue quickly releases tissue factor and other stimuli, such as expelled collagen, to activate a variety of physical mechanical, biological or chemical events. These changes cause damage to the nerve fiber and even peripheral vascular disease, which in turn takes its toll at the molecular level. Endothelial dysfunction is the most serious impairment affecting microcirculation, owing to changes in the proliferation of endothelial cells, thickening of the basement membrane, decreased synthesis of nitric oxide, increased blood viscosity, alterations in microvascular tone and decreased blood flow. On the other
hand, the immune system is compromised by lowered leukocyte activity, inappropriate inflammatory response and the disruption of cellular immunity (inhibition of fibroblast proliferation and impairment of the basal layer of keratinocytes, reducing epidermal cell migration). (Aguilar F, 2005, Boulton AJM, 2003)

Fig. 1. Role of different mechanisms in neuropathy. The most important are oxidative stress and endothelium dysfunction; these mechanisms produce disorders in metabolism and microcirculation. EDFH= Endotelium derived hyperpolarizing factor, NBF=nerve blood flow, NGF=nerve growth factors NVC= Nerve velocity conduction, PXG= Glutathion Peroxidase, SOD= Superoxide Dismutase (Modified from Aguilar R, 2009a).

Another important factor that affects neuropathic foot microcirculation is the disability of the nerve axon reflex. The stimulation of the C-nociceptive fibers produces retrograde stimulation of adjacent fiber (Caselli A, et al, 2003). These fibers instantly secrete a vasomodulator, such as substance P (SP), a calcitonine gene-related peptide (GCRP), neuropeptide Y (NPY), and histamine. These peptides produce vasodilation (this response is known as Lewis Triple Flair Response) (Lyons 2008). The Lewis response mechanism is: red spot due to capillary dilation, flare due to redness in the surrounding area, in turn due to arteriolar dilatation mediated by axon reflex and wheal due to exudation of fluid from capillaries and venules, drawn up in Fig 2 for normal and diabetic patients.

The main substances are histamine and peptides. In the absence of this response the skin blood flow is affected when the injury occurs and this is one of the major factors related to impaired wound healing (Parkhouse N, 1988).
2.2 Anatomical and structural alterations

The anatomical and structural alterations that are the result of diabetic neuropathy are divided into three types: sensory, motor and autonomic.

2.2.1 Peripheral sensory neuropathy

Close to 30-50% of all diabetic patients present peripheral sensory neuropathy. Sensory neuropathy is the most common predictor of foot ulceration in a patient with diabetes (Nather et al., 2011). The development of foot ulceration reported in sensory neuropathy occurs in 78% of cases. Peripheral sensory neuropathy initiates a series of events that together with peripheral motor and autonomic damage eventually result in foot ulceration. In a normal situation, treatment centers would tell the patient to continue walking or walk some with changes in gait. The recipients of this information are the sensory nerves. In diabetic foot, sensation is affected and the stimulus to refrain from ambulation does not exist. These are the causes that lead the patient to continue walking even when no sensation of pain is present, which in turn prolongs affectation and delays healing of the traumatized area. The damage to sensation that provides protection is the key element in the development of ulcers (Reiber GE., et al 1999).
2.2.2 Peripheral motor neuropathy

Motor neuropathy typically presents structural alterations of the dynamic anatomy of the foot and joints, causing weakness and wasting of small intrinsic muscles. This causes a loss of balance in the gait because of damage to the muscles, as mentioned above, in addition to another characteristic: clawing of toes and plantar flexion of the metatarsal head (Carine HM et al 2004). The atrophy of the interosseous and small intrinsic muscles of the foot acts to stabilize and hold the phalanges of the toes straight, as the long flexor and extensor tendons act through the insertions into the distal phalanges of the toes up into dorsiflexion, similar to a foot pressing the accelerator of the car.

Alterations in the morphology of the structure of the foot, toes, forefoot and limited joint mobility impaired the ability of the foot to absorb and redistribute the forces relayed to impact the ground while walking. Effects on the foot include the reduction of motion and changes to the angle of the subtalar and first metatarsophalangeal joints (MTPJ). Vital musculoskeletal structures, such as equinus deformity through the shortening of the Achilles tendon and the collapse of the plantar fascia, facilitating abduct to adductor equine changes to the forefoot. In diabetic patients, the flexor tendons and extensor tips tend to be straight and rigid. If the intrinsic muscles are unable to do this, the toes shrink back to form what is called hammer toes and favor the thrust of one toe over another or a toe on the metatarsal head with the weight forced to the anterior surface with high force.

On the other side, the contraction that the hammer toes causes on the plantar fat pad and the metatarsal heads reduces soft tissue plantar MTPJ, making them more susceptible to fracture of the skin, including the bone next to the formation of traumatic ulcers, owing to inappropriate weight loads. The mechanism is related to the high pressure exerted on the foot that occurs during the gait, in turn caused by motor neuropathy, which itself in turn causes structural changes in the anatomy and sliding of the fat pads of the foot, in addition to occasional blows received.

Fig. 3 presents three different images at different stages of changes in architecture of the foot, allowing us to better understand the condition. In addition to the shortening and thickening of the joints, the decreased capacity of distribution of plantar pressure in DM patients contributes to the development of high foot pressure and ensuing ulcerations. Excessive pressure and structural deformities in individuals with neuropathy is a prerequisite for the development of wounds. Consequently, structural changes and offload pressure favors the formation of calluses on various prominent parts of the foot, including the plantar region, the heel, the big toe, etc.

The structure of the foot is a major determinant of plantar pressure. Although some structural factors are independent of the DM, others are predisposed to high pressure and appear to be a consequence of the disease. Obviously, the major collapse is seen in Charcot neuroosteoarthropathy in which foot fractures lead to increased pressure. (Lyons et al., 2006). A significant reduction of plantar soft tissue thickness is seen in diabetic patients with a form of neuropathy such as rheumatoid arthritis. Metatarsalgia is a common, frequent symptom of offloading of MTPJ with pressure on the head of the first metatarsal (MTT). It could explain almost 70% of the variation in plantar pressure in the joint on the thickness of soft tissue (Schie CHM, & Boulton. 2006).
It is necessary to clarify the concepts that influence structural and biomechanical abnormalities (Fryckberger RG, et al 1998, Lawrence L, et al 2008) as shown schematically in Fig 3.

**Clawing toes**: hyperextension of MTT phalange joints, usually accompanied by cavus foot and calluses on the dorsal surface of the fingers and the plantar surface of the metatarsal head or the tip of fingers.

**Cavus Foot**: under normal conditions the foot is shaped convexly due to the longitudinal medial arch that is extended from the head of the first MTT and the calcaneus; if this arch is abnormally high it produces an abnormal distribution of weight loads, favoring the formation of calluses in the forefoot and rearfoot.

**Equinus Deformation**: shortening of Achilles tendon (three muscles: lateral, internal gastrocnemius and soleus), falling of plantar fascia and facilitating abduct or adduct in the forefoot, beside the lost at the long flexor and extensor tendons that produce dorsiflexion.

1st toe rigid: it is due to hardening of the first MTT phalange joint with loss of dorsiflexion, resulting in excessive weight forces on the plantar surface and callus formation.

**Joint stiffness**: The limitation of joint movement is produced by the glycosylation of collagen and thickening of periarticular structures (tendons, ligaments, joint capsule, etc.) which favors deformities and plantar pressures, upsetting the biomechanics of the foot during walking by limiting plantar flexion and promoting equinus foot.

Fig. 3. The different deformities of “at risk” diabetic foot. The three different stages of changes in the architecture of the foot which causes hammer toes and contraction of the plantar fat pad (look arrow). Above: normal foot. Middle: beginning of deformation. Bottom: Complete deformation. *(Modified from Levin & O’Neal 2008. Right images courtesy from Ramos F, MD)*
**Deformity of the nail**: Thickening or deformity of the nail atrophies the nail plate with convex deformity, causing pressure on the ridge tissues and, in turn, ingrown nail. The nail flange forms a callus in response to pressure and inflammation. As a result the tissue of the trauma may become ulcerated and infected and penetrate the nail flange.

### 2.2.3 Autonomic neuropathy

Autonomic neuropathy is common in longstanding DM. In the lower extremities, autonomic neuropathy may result in arteriovenous shunting, resulting in the dilation of small arteries and producing distension of the foot veins, not alleviated through elevation of the foot. Consequently, neuropathic edema hinders treatment through diuretic therapy. Neuropathic feet have a tendency to swell and to feel warm as a result of arteriovenous shunting. Autonomic neuropathy results in decreased autonomic nerve roots that innervate the sweat skin glands with appendage tissue, causing dryness of the skin and decreased elasticity, especially from the middle third of the leg down, where there is also discoloration of the skin shown in Fig 4. Dry, stiff skin produce cracks more easily forming splits, fissures or fractures of the skin and callusing around the foot injury, more frequently in the heel rim, plantar medial and first MTP -especially during the dryer months, as observed in both images of Fig 5. The first one (A) shows the first stages and the second one depicts the final stages. These fractures or skin fissures can become infected, resulting in local cellulitis and then on to small longitudinal ulcerations. (Aguilar R, 2009)

![Fig. 4](image-url) 

Fig. 4. Lower extremities of a patient with DM presenting the 3 types of neuropathy: sensitive (pain, burning, disesthesias, numbness), motor (cavus foot and claw toes) and autonomic (dry skin, absence of hair, changes in skin color). (Courtesy of Aguilar F & Terán JM, 2011)
2.3 Environmental influences

Environmental influences acutely and chronically accelerate ulceration, starting with lesions in the soft tissue followed by stratum corneum of the skin, subcutaneous tissue, muscle and fat pad.

2.3.1 Limited joint mobility

Restriction of joint mobility is a part of diabetic neuropathy, related mainly to collagen glycosylation that results in thickening of the periarticular structures such as tendons, ligaments and joint capsules. At the foot level, all joints may be involved – ranging from the talar, subtalar, MTPJ, to flattening of the arch or pronation. These structures absorb the shock of gait, and reduce and attenuate ground reactive forces. In diabetic patients the absence of this mechanism impairs the ability of the foot to adapt to the ground surface and absorb the shock that develops when the heels make contact with the ground during walking. High pressure develops more in the forefoot area, consequently becoming an additional factor in the development of foot wounds (Pham HT et al., 2000).

The footwear designed in diabetic patients reduces the risk of foot ulcerations. We recommend the design and manufacturing of footwear and other items designed to potentially reduce foot pressure in neuropathic feet and offloading, thus redistributing and reducing foot pressure in areas that are prone to ulceration. Shoes are an important consideration for patients that are at risk for foot ulcerations (Sicco A, et al 2011).

2.3.2 The gait

Diabetic ulcers can occur anywhere on the foot but clinically the most frequent presentation is on the plantar surface. This predilection of diabetic ulcer on the plantar surface is related to the trauma that is developed in this area due to increased discharge pressure on the plantar surface during walking. Under normal conditions the foot has the ability to distribute the load equally over the entire surface - the forefoot, middle foot and rear foot - consequently preventing the development of ulcers. This capability is lessened in diabetics, first of all because of changes in the architecture of the foot related to the fundamental motor neuropathy that produces disorders in the mobility of joints, limited both by neuropathy as well as by the metabolic changes producing glycosylation of the collagen structure through a covalent bonding process which increases the rigidity of the ligament structures, tendons, and the joint capsule of both the subtalar and metatarsal region. Additionally, there is decreased mobility of the Achilles tendon, in turn creating an equinus deformity that directs plantar forces to the region of the forefoot. As a result of these changes, the pressure of certain areas of the foot is considered at high risk for producing a tissue injury, even after walking short distances. It is important to note that the presence of sensory neuropathy in a patient at risk and using inappropriate shoes will induce injury of the subcutaneous cellular tissue during the gait, compromising the integrity of skin tissue; this, together with the absence of pain, is conducive to the onset of foot ulceration (D'Ambrogi E et al., 2003).

These 3 dimensions (physiopathology, anatomical and structural alterations, and environmental influences), contribute to the formation of ulcers. The dimensions are integrated by 2 mechanisms:
Fig. 5. Two different feet with “cavus foot”. (A) Cavus foot with skin hydrated (first stages). (B) Cavus foot with dry skin, fissures, peripheral vascular disease and ulcered ankle. (Courtesy of Aguilar R & Terán JM, 2011)

Table 1. Risk factors for the development of ulcers (Modified from Lipsky 2004).

- **Internal mechanism**: Associated with structural deformities of the foot anatomy which are favored by sensory, motor and autonomic neuropathy disorders. Together, limited joint mobility and structural alterations are caused by glycosylation of collagen and thickening of the periaarticular structures that are produced for a disorder in the production of elastin (tendons, ligaments, articular capsule and, etc.), at subtalar, metatarsal and metatarsophalangeal head levels. Because the diabetic condition invariably
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involves hyperglycemia, non-enzymatic glycation of collagen and a deterioration of elastin, fibronectin, proteoglycans, epithelial cells and other proteins are noteworthy in wound healing during repair sequence (Ahmed N 2005, Huijberts MS 2008).

- **External mechanism:** Related to chronic trauma of the soft tissues of the foot that precipitate the onset of an injury on the same structures that later produce the wound.

These mechanisms, together with risk factors, do not act independently to cause ulcers. They require the combination of numerous events (sometimes fewer than others) to produce wounds in different areas of the foot, different sizes and different components. In fact, the most important factors that produce foot injury and lesion of the extracellular basement matrix of the skin are: neuropathy, deformity, trauma, peripheral circulation failure, inflammation, dryness and calluses on the foot (Boulton AJM 2006).

The accumulation of the principal components corresponds to the causal pathways that result in diabetic foot ulcer when applying the Rothman model of causation (Reiber GE 1999). These factors that are insufficient on their own, combined will ultimately result in the formation of a diabetic foot ulcer; the interaction of a number of component causes may result in sufficient cause for ulceration, as shown in Fig 6. The most common causes interact between one another to result in ulceration in the diabetic foot. These risk factors are: neuropathy, deformity, trauma and impaired healing (present in 63% of cases) (Pecoraro RE, 1990).

Fig. 6. **Sufficient cause.** The factors that comprise sufficient cause for ulceration are: neuropathy, deformity, trauma, and impaired healing. It is imperative that the 4 factors be present to create sufficient cause. If any of the factors is absent, the ulcer cannot be formed (Modify for, Lyons 2008, Boulton 2006, Ziegler 2003)
The classical example is a patient with insensitive feet who buys shoes too small that traumatize the feet with maximum pressure exerted on different points caused by the tight fit, as shown in Fig 7. In our experience, neuropathy was the first component cause (present in 100% of patients with ulcers), and the ischemia was a component cause in 35% of ulcers. Another independent component of the triad is the difficulty of healing the ulcer that is related with alterations in the immune response, decreased blood flow to the wound area, cellular components of the inflammatory system, abnormal expression of growth factors, cytokines and their receptors that are involved in the healing process; it is usually the combination of the various components that leads to chronic ulceration and amputation.

Fig. 7. Diabetic patient with neuropathy, callus and claw toes using inappropriate shoes that cause repetitive trauma, thus forming the fracture of the callus and infecting the skin. The final result is a wound that later evolves to an infected ulcer. Sufficient cause is complete. (Courtesy of Aguilar F & Terán JM 2011)

3. Clinical presentation

About 50% of patients with foot ulcers due to DM present clinical signs of infection. By definition, infection is characterized by the presence of purulent secretions or at least two of the classic signs of inflammation (erythema, hyperemia, edema, or swelling and pain) but these data can be masked by lack of the sensitivity in the patient due to sensory neuropathy or impaired immune response. It is also common that patients with infection are associated with poor metabolic control. Therefore, we must take into account other aspects of infected ulcers due to diabetes, including lack of granulation tissue, delayed healing or odor.

The prevalence of ulcer is highest in the presence of neuropathy, anatomical disorders, structural and environmental factors such as offloading, high-pressure processes on the plantar foot, the forefoot, midfoot, rearfoot and especially the metatarsals heads. These overloads on the limb associated with limited joint mobility lead the plantar fascia to undergo changes, such as shortening and thickening that can cause a skin fracture due to poor quality of skin in this area (callused, thick, dry, etc) causing their own skin germs to progress or introduce bacterial into the skin cracks and potential progression over time resulting in critical colonization (presence of at least 100,000 bacteria per gram of tissue) and finally culminating in infection (Lipsky BA, & Berendt AR 2006).

It’s important to consider that pain is not a prominent sign in patients with infected diabetic foot owing to the loss of sensitivity caused by affected short and long fibers (A-beta and A-delta) secondary to hyperglycemia. In the same way, we have to consider a possible

The molecular pathways that are involved in the ulcer formation are:

1. The ulcer develops because structures of connective tissue fail.
2. Absence of an important matrix of cellular organization resulting in deterioration in the protection of normal epithelial growth.
3. Reduced angiogenesis and fibroplasia.
4. Persistence of inflammatory cells, neutrophils or macrophages, which act in an appropriate immunological environment.

Table 2. Record the characteristics of the wound in every exam of diabetic foot (every week). This decalogue helped to evaluate ulcer evolution, prognosis and the healing process. PEDIS (*): see table 3, Wagner (**): see table 4 and San Antonio (***): see table 5. (Courtesy of Aguilar R & Terán JM).
The elements listed above persist and lead to deterioration in the integrity and restoration of tissue, resulting in a chronic ulcer with persistence of bacterial infection, which alone stimulates an inappropriate inflammatory cellular response. There is also a chemical injury that leads to loss of oxygenation with absence or decrease of tissular perfusion, local cellular ischemia and tissue necrosis or death.

If the trauma persists and overload pressure continues, the healing of the ulcer is delayed due to failure in the formation of granulation tissue and to the development of epithelial tissue. At this point proteolytic degradation surrounding the injury is the most important cause of secretion of proteins, including elastase, protease and metalloproteinase, capable of degrading not only the adhesive substrate for cell migration but also signaling molecules that would promote wound healing, such as development of growth factors and cytokines.

In conclusion, the accelerated proteolysis can cause a high level of breakdown products of connective tissue cellular processes that activate inappropriate inflammation. That's why the necrotic tissue should be debrided extensively and aggressively from the start of ulcer treatment, as this tissue is a negative factor in the wound healing, with difficulty due to the high content of substances mentioned above (Davidson JM, & Di Pietro L 2006; Cooper DM et al 1994; Sheehan P et al 2006).

4. Diabetic foot infections

In diabetic patients with foot wounds, the physician should perform a systematic examination to determine if the wound is infected and the degree of severity of said infection. The examination should start with vital signs, consciousness, complete review of the limb to the foot end, always removing the patient’s shoes and socks, and should include a neurological, vascular, dermatological and musculoskeletal examination to determine the external characteristics of the skin, the shape and structure of the foot and alterations in the fingers, protruding metatarsal, heel, etc. The physician should also perform an instrumental exploration, neurological reflex hammer, tuning fork 128 cycles, 10 gm monofilament, thermograph, etc, Table 6. A clinical vascular examination will focus on the search for foot pulses. All this will determine the stage of neuropathy with or without ischemia. Fig 8 (American Diabetes Association (ADA) 2011)

After locating the ulcer, evaluate the wound characteristics, just as proposed in Table 2, (number of ulcers, depth, size, color, exudation, edges, adjacent skin, maceration, pain, infection, etc.). In most cases an x-ray should be taken to dismiss presence of gas, or a foreign body or osteomyelitis. During initial ulcer debridement, look for aerobes and anaerobe organisms. As concerns a blood test, we recommend a complete blood count, blood chemistry and if it is considered prudent speed glomerular sedimentation and reactive “C” protein (Eneroth M, & Larsson J, & Apelqvist J 1999; Kaleta JL, & Fleischli JW, & Reilly CH 2001)

This complete examination will help the doctor to draw up a clinical classification of the degree of infection (mild, moderate or severe), table 3, as well to evaluate the depth, extension, table 4, and ischemia with presence of infection, table 5. The severity ratings guide us to reference the patient to further hospital care, and start empirical implementation of antibiotics. The types of diabetic foot infections can start from a simple paronychia,
onychomycosis, cellulitis, foot infection, deep tissue infection, septic arthritis, osteomyelitis, necrosis or gangrene. Infections can be painless, persist for days, weeks or months and progress rapidly even in a few hours. Bed debridement, incision and drainage of the ulcer will be necessary in most circumstances. (Lipsky et al 2004)

![Diabetic foot infection](image)

**Fig. 8.** Diabetic foot infection for insensitive repetitive trauma. The wound is close to deep tissues, involving bone as well. This patient need antibiotics and appropriate debridement (Courtesy Aguilar F & Terán JM, 2011).

<table>
<thead>
<tr>
<th>Clinical manifestation of infection</th>
<th>PEDIS*</th>
<th>Wagner**</th>
<th>San Antonio***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound lacking purulence or any manifestations of inflammation* *, ***</td>
<td>Uninfected</td>
<td>1</td>
<td>1**</td>
</tr>
<tr>
<td>Presence of &gt;2 manifestations of inflammation:</td>
<td></td>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Purulence</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Erythema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tenderness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warmth or induration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>But any cellulitis/erythema extends &lt; 2 cm around the ulcer:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection limited to the skin or superficial subcutaneous tissues** , ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No other local complications or systemic illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection (as above) in a patient who is systemically well and metabolically stable but which has &gt; 1 if the following characteristics:</td>
<td>Moderate</td>
<td>3</td>
<td>4**</td>
</tr>
<tr>
<td>Cellulitis extending &gt; 2 cms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lymphangitic streaking</td>
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<td></td>
<td></td>
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<tr>
<td>Spread beneath the superficial fascia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep tissue abscess ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gangrene **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involvement of muscle, tendon, joint or bone* *, ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection in a patient with systemic toxicity or metabolic instability (fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia or azotemia)</td>
<td>Severe</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Table with PEDIS* grade of foot infection correlated with the most common classic scales for wounds (Wagner** and San Antonio***). Each item “asterisk and color” was selected according to the scale *(modified from Lipsky BA 2004)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Pre-post-ulcer lesion without skin break</th>
<th>Superficial Ulcer</th>
<th>Deep ulcer (tendo/capsule)</th>
<th>Wound penetrating bone/joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
<td>+infection</td>
</tr>
</tbody>
</table>

Table 5. San Antonio scale. (Infection and Ischemia) (Armstrong et al, 1998)

<table>
<thead>
<tr>
<th>Level of evaluation, by area(s) to be assessed</th>
<th>Relevant problems and observations</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Fever, chills, sweats, vomiting, hypotension, and tachycardia</td>
<td>History and physical examination Serum chemistry and hematological testing Assessment of mental status Interviews with family and caregivers</td>
</tr>
<tr>
<td>Limb or foot</td>
<td>Loss of protective sensation. Motor and autonomic exam. Pain (burning, shooting, stabbing pains like pins and needles)</td>
<td>Pin prick test, &quot;light touch, cotton wisp, vibration test (128 Hz tuning fork), pressure perception (50 g monofilament), ankle reflex, plantar and Achilles, thermograph.</td>
</tr>
<tr>
<td>Wound</td>
<td>Necrosis, gangrene, foreign body, and involvement of muscle, tendon, bone or joint</td>
<td>Inspect, debride, and probe the wound deep and X-ray foot Gram staining and culture ultrasonography or CT for detection of deep abscess, and radiography and/or MRI for detection of osteomyelitis.</td>
</tr>
</tbody>
</table>

Table 6. Evaluating the diabetic patient who has an infected foot (Lipsky et al, 2004 modified for Aguilar & Terán 2011)
4.1 Evaluating the diabetic patient who has an infected ulcer

All diabetic foot infections require antibiotic treatment. However, not all ulcers are infected from the beginning and therefore do not require antibiotics. The main premise is that antibiotic treatment will be used to clear up infection and not for wound healing, which takes longer (Lipsky BA, 1999). Take into account the following aspects to choose the right antibiotics:

1. Understand the microbiology of the wound, starting with broad-spectrum empirical therapy for moderate and severe infections and a relatively small range for moderate infections. We can’t forget factors such as recent antibiotic use, exposure to hospital facilities and local antibiotic susceptibility.

2. The route of administration is of great importance for the success of treatment; for serious infections the recommended route is parenteral, and mild to moderate infections can start with oral or parenteral impregnation treatment for further oral treatment, adjusting to highly bio-available drugs like quinolones and the oxazolidinones.

3. The duration of antibiotic treatment should be determined according to the severity of the infection; mild infections only require 2 to 4 weeks, severe infections may require 6 to 12 weeks or more. Unfortunately in severe infections the amputation of part or the entire foot is a high probability.

4. The selection of a specific agent or combination of antibiotics is based on the considerations discussed above and the condition of each patient (renal failure, allergies, etc.), restrictions of presentation, convenience and monetary cost. (Lipsky BA, Berendt AR 2006)

5. Basics measures in the treatment of diabetic foot

The treatment of foot ulcers in diabetic patients varies constantly depending on the severity of the ulcer and the presence or absence of ischemia. However the basic points of treatment are:

- Debridement in case the ulcer presents thick edges or necrotic tissue.
- Reduction in overload pressure.
- Complete rest of the foot (orthotics).
- Treatment of the infection.
- Local wound care.

To start this care we require the knowledge of the patophysiology listed above in relation to wound healing. The care and products that have shown to improve wound healing are:

1. **Debridement** - The goal is complete debridement of all necrotic tissue with impaired vascular and non-viable tissue, large incision and maintain good drainage when necessary in order to allow a granular bed and a better flow of the wound.

2. **Reduced offloading** - Reduction of pressure is essential in the healing of foot ulcers; as has been said, ulcers occur in areas of high pressure on a foot without sensitivity or with damaged sensitivity. There are several methods to reduce the pressure; the most popular includes mandatory resting of the foot with a cast and other new light materials, special shoes, leg braces and bandages using felt and/or foam.

3. **Treatment of Infection** - The ulcers that are already colonized with bacteria serve as a port of entry to further infection. The diagnosis of infection is first based on clinical
appearance and cardinal symptoms (erythema, edema, pain, tenderness and warmth). Meanwhile, care must be taken, aside from the bacteriological diagnosis, to treat cellulite, start antibiotics empirically and request the necessary x-rays employing the most advanced techniques available to reject the possibility of abscess with osteomyelitis (such as MRI or CT scan of the foot). **Tables 7 & 8.**

4. **Wound care.** The effective use of bandages is essential to ensure optimal management of foot ulcers in diabetic patients, applying the concepts of cleanliness, humidity and proper environment for wound healing to prevent tissue dehydration and cell death, accelerate angiogenesis and facilitate the development of growth factors with the epithelial cells resulting in less discomfort for patients.

5. **Products for advanced wound care:** These products have been developed in response to an improved understanding of the holistic healing of injured tissue in diabetic foot ulcer. A greater knowledge of the patophysiology of wound microenvironment deficiencies decreased development, growth factors, inactivity, altered cell, to the development of products to correct these deficiencies. These include human growth factor platelet derived, Epidermal growth factor recombinant human DNA (Heberprot-P®), colony stimulating factor granulocytes, biological cultivate skin substitutes (Dermagraft®, Epifast®) hyperbaric oxygen, larva therapy, etc. (Boulton JM 2003)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Foot Infection</th>
<th>Pathogen Microorganisms</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Involved soft tissue only</td>
<td>Cellulitis with/without open skin. Infected ulcer was previously treated with antibiotics therapy.</td>
<td><em>β</em>-hemolytic streptococci, <em>Staphylococcus aureus</em> and <em>enterobacteriaceae</em> (groups A, B, C and G).</td>
<td>1-2 weeks; may extend up to 4 weeks if allowed to resolve.</td>
</tr>
<tr>
<td>B. Involved infected skin tissue, subcutaneous tissue, muscles, joints (but no bone.)</td>
<td>Ulcer that is macerated of soaking polymicrobials.</td>
<td><em>Pseudomonas aeruginosa</em> (often combined with other organisms) often polymicrobial.</td>
<td>3-4 weeks; sometimes may needed extend 6-8 weeks to resolve.</td>
</tr>
<tr>
<td>C. Involved residual infected tissue (still viable), muscle, joints, ligaments (with or without bone)</td>
<td>Long duration non-healing wound with prolonged broad spectrum antibiotics therapy.</td>
<td>Aerobic gram- positive cocci (<em>Staphylococcus aureus</em> coagulase negative, <em>Staphylococci</em> and <em>enterococci</em>), diphtheroids (* Corynebacterium spec*), <em>enterobacteriaceae</em>, <em>Pseudomonas species</em>, non fermentative Gram negative, <em>rod</em> and possible fungi with possibly anaerobes species (more frequently <em>bacteroides fragilis</em>).</td>
<td>4-8 weeks; may extend 5-12 weeks if can resolve. High risk to partial amputation.</td>
</tr>
<tr>
<td>D. Residual tissue and bone is death.</td>
<td>“Fetid foot” extensive necrosis or gangrene, malodorous.</td>
<td>Mixed (Gram positive cocci, Gram negative cocci) and including <em>enterococci</em>, <em>enterobacteriaceae</em>, non fermentative Gram negative rods and obligate anaerobes pathogens.</td>
<td>12 weeks or more with high risk to amputation (some part or entire foot).</td>
</tr>
</tbody>
</table>

*Gram negative: Bacteroides fragilis, vulgatus, ovatus, distasonis, vulneris, gracilis.*

**Antibiotic resistance species.** For example: meticillin resistant *S. aureus*, Vancomycin resistant enterococci or extended-spectrum B-lactamase produce Gram-negative rods are common.

Table 7. Pathogens associated with various clinical foot-infection syndromes. (Modified from Lipsky 2004)
Table 8. Suggested empirical antibiotic regimens accord the severity of disease. *recommended by the authors (Aguilar & Terán 2011). ** For patients in whom methicillin-resistant *S. aureus* infection is proven likely. (Lipsky 2004).

### 6. Ulcer recurrence

The clinical evaluation of patients with diabetes, particularly in the assessment of the foot should be referred to the history of previous ulceration or amputation. A history with a record of ulceration or amputation increases the risk of a future return of ulceration, infection and amputation. Above 60% of diabetic patients with a history of foot ulcer may develop another ulcer within a year of healing ulcers. (Luca DP 2003)

There are 3 possible explanations:

1. Risk factors that caused ulceration in the first place in many cases will be still present.
2. The skin and soft tissue at the site of previous ulceration do not retain the same properties after healing compared with the conditions they had before the ulcer. Thus, the skin and soft tissue, after the ulcer is healed, are more fragile and break more easily, as shown in Fig 9.
3. Areas of previous amputation can leave residual deformities which in themselves are areas of increased pressure that may lead to ulceration. In addition, any previous surgery can alter biomechanics, leading to irregularities of the gait and imbalance where high pressure areas will develop new ulcers in the future.

A musculoskeletal examination will allow us to understand the structure and dynamics of the forces of the foot. The presence of foot deformities, joint mobility and their limitations must be recorded as both increased pressure and the cause of foot ulceration. Bone prominences can be observed on second plane as Charcot osteoarthropathy, motor neuropathy, foot deformities, hallux valgus limitus-rigiduz and hammer toes. Also, in the plantar region there may be callus formation, as we now know that many of these calluses are focal areas of increased pressure that can lead to a potential site of ulceration. Any area of erythema owing to the use of inappropriate shoes should be protected with padded patches and as soon as possible changed to proper shoes to relieve the pressure (Abbott CA & Carrington AL, & Ashe H, et al. 2002).

Fig. 9. After the wound is healed, the patient needs to protect the foot due to changes in the architecture and labile skin in order to prevent ulcer recurrence. The use of orthetics, correct shoes, special socks and rehabilitation of the foot is a priority (Courtesy of Aguilar F & Terán JM 2011).

7. Conclusions

Despite progress in knowledge regarding the pathophysiology of ulcers, the mechanisms involved nowadays are not completely clear. The main mechanisms: neuropathy, deformity and trauma along with physiopathogenic information at the molecular level and knowing the structural and anatomic alterations (clawing toes, hammer toes, cavus foot, equinus foot, etc), are all important to draw up strategies for treatment and prevention. This information is summarized in Fig 10. On the other side, offloading increases pressure on the foot, thus leading to alterations in environmental factors such as gait, instability and limited joint mobility. All of this suffices to explain the changes in the architecture of the foot and this, in
turn, allows for drawing up prevention policies. Changes in the microcirculation of the foot in patients with diabetes remains one of the major causes of difficulty in wound healing associated with thickening of the vascular endothelium, the release of vasodilator substances and the participation of endothelial cells in angiogenesis and reparative processes of the wound. These together represent the most advanced knowledge available at the molecular level. The vasodilatation depending on the endothelium cell reduces the expression of nitric oxide synthase which further deteriorates the microenvironment of the wound. More recent mechanisms, such as the knowledge of the deterioration on the nerve cell particularly the reflex nerve-axon, coupled with changes in the polymerase activity (ADP ribose) and the increase of the formation of nitrous tyrosine give us hope for the future of healing ulcers. A better understanding of cellular changes and the interplay between formation of connective tissue, collagen tissue formation (collagen is part of the skin, bone, tendons and ligaments) the expression of growth factors and cytokines are involved in tissue repair of wounds in people with diabetes as shown Fig 10. In addition, we proposed increased care in early injury or trauma and prevention of use of inadequate shoes and offload pressures to stop formation of ulcers. If ulcers do form, adequate treatment, foot care and complete rest for the foot could prevent amputation. Fig 10 (red)

It is clear that the spectrum of treatment of diabetic foot ulcers requires the participation of several specialists. Foot ulcers are not the responsibility of a single medical professional, they are the responsibility of a multidisciplinary team working for the care and healing of foot ulcers. On this team we can find first contact physicians, surgeons, orthopedic, vascular surgeons, podiatrists, neurologists, endocrinologists, orthotics, specialist nurses and all practitioners and specialists interested in the care and attention of the foot. In this chapter we have tried to give a clear, complete and current vision of the management of ulcers in diabetic patients by detecting and treating risk factors at an early stage, directing the entire team of health professionals as one would an orchestra in which the symphony focuses on sparing the patient with diabetic foot from dire consequences.

7.1 What is expected for the future?

There are various factors that will work together to improve wound care in the next few years. We must urge scientists, clinicians and even government regulators to get involved in the control of diabetes mellitus and wound healing. The problem is overwhelming worldwide and demands greater attention focusing on the occurrence of diabetes morbidity and mortality. Diabetic wounds continue to spiral out of control. New trends show interest and progress in the biology of healing and wound care. There is a great deal of exciting science and work done that has defined some of the basic pathogenesis of chronic wounds. This can be divided into the biological scientific and technical care of wounds.

7.1.2 Biological scientific

1. **Modulation of temperature.** Recently advances with modulation of temperature to control pressure of diabetic foot necrosis prevent cell death and progression of the ulcer formation in patient with DM. Cooling as well as pressure relief will be an important tool in the management of diabetic foot wound. With this measure we can to prevent the inflammatory changes due to the pressure and the flow-reflow phenomena.
Fig. 10. This algorithm summarize all events that are at play in the development ulcers and potential amputations. Prevention is the key. (red block)
2. **Proteases.** The early inflammatory response of diabetic foot wounds produces excessive proteases. Although the protease issue is relevant, it is only the tip of the iceberg. The healing of the wound requires angiogenic factors and these are destroyed by proteases. New therapy would be enhancement of endogenous antiproteases in order to improve healing. Another important issue is the control of free radical production by polymorphonuclear leukocytes (PMNs) as free radicals stimulate inflammation and increase proteases.

3. **Oxidative Stress.** Although there are many metabolic disturbances that occur in DM, the oxidative stress (OS) play an important pathogenesis roll of a numerous mechanisms in DM and diabetic neuropathy. Diabetes contributes both directly and indirectly to increased oxidative stress. Thus, there is elevated production of reactive oxygen species (ROS) and a reduced endogenous capacity of free radical cell scavengers. Contributors to the increased oxidative stress include auto-oxidation of glucose and its metabolites, advanced glycation, mitochondrial abnormalities, ischemia reperfusion, microvascular damage, and enhanced flux through the polyol pathway. OS produce endothelium dysfunction, and diminishing nitric oxide release. Alpha lipoic acid in combination with arginine and citrulline increase nitric oxide, reduce OS by both benefits improved free radical scavenger and metal chelator. Besides, there is evidence that improved nerve functional deficit, endoneural perfusion and vascular bed perfusion and the microcirculation and capillary blood perfusion. Nevertheless antioxidant vitamins potentially improve healing of the wound.

4. **Gene therapy.** We are still grappling with this area of medical knowledge. On the other hand, this care is expensive, though we expect that we will see cost-effective gene therapy in the future. The focuses are: stimulating growth factor production and gene therapy to inhibit proteases to permit growth factors to work well.

5. **New drugs to treat diabetes.** The best option is to keep blood sugar within normal range; this produces less glycosylation of all sorts of tissues in the body, reducing diabetic complications.

6. **Education.** Continuing medical education (CME) is important to every professional to treat DM. CME needs to develop strategic projects to stimulate initiatives for early prevention and detection of complications in DM and neuropathy. Updated medical information needs to cover all news about nutrition, hypertension, obesity and dyslipidemia (metabolic syndrome).

7.1.3 Technical care

1. **Industry.** The relevant industry must listen to scientist and improve the quality of studies and on a scientific basis produce potential products for clinical application.

2. **Wound healing centers.** The concept of the wound healing center is excellent if we have evidence and monitoring of formal education for health care providers at these centers and implement frequent reviews and updates.

3. **Progress in communications.** We live in an era in which computerized communication is superb, yet we have not taken advantage of this benefit for our patients, especially for wound healing. Google®, PubMed®, Cochrane® and the American Diabetes
Association journals database are a big help for medical information and updates. The team of wound care health workers needs to have readily accessible information. Being a doctor is hard work, but part of this work is being updated through new technologies.

4. **Emotional aspects.** Every patient needs to be referred to psychological specialists so as to better handle their emotional problems, equally important as the physical aspects. Everyone on the team is involved in the pathological process and must heed details. The initial assessment of the DM patient with neuropathy and ulcer demands a thorough examination and MUST ALWAYS include a careful foot exam after removal of shoes and socks. Additionally, the exam includes: inspection of foot deformity, pressures, neurologic exam, vascular exam, monofilament, vibration and so on. It is surprising to note how many patients seek expensive, inadequate, quack or esoteric therapies in an attempt to save their leg.

5. **Federal Government Policies.** The federal government should be more involved in supporting scientific and clinical projects and encouraging medical prevention in all communities in countries with a high prevalence of this disease, such as Mexico.

6. **Education.** Many courses on wound healing it are necessary to disseminate and updated information, to offer clear ideas and give practical advice. Regrettably, there are even national conferences in which there is an absence of information about new concepts on wound healing, proper evaluation and treatment. There is a window of opportunity here.

7. **Offloading the diabetic foot:** New role of footwear. Several methods of measuring and reducing foot pressure include new advances but we need to be aware of their limitations. Extra-deep footwear, jogging shoes, hosiery, insoles, and orthotic hosiery have been shown to decrease plantar foot pressures. Furthermore these devices can prevent the occurrence and recurrence of foot ulceration. Research at present is still in the initial phase of developing methods and measuring shoe shear forces. Piezoelectric transducers are currently being evaluated; these may be able to measure both vertical and shear forces in the near future.

8. **New devices**

Actually in some countries are available some systems to promote the support of wound healing such as the negative pressure wound therapy (V.A.C®), the wound cleansing and debridement system (Jetox®) and the infrared therapy system (Anodyne®).

The process in wound healing is a cascade of inflammatory reactions and cellular interactions. Modern technologies are focused on reversing this unfortunate complication. For that reason we propose the points mentioned above in technical care. The science, knowledge and practice are attempting to promote vascularization, devices and molecules of tissue growth and a better understanding of pathophysiology of the wounds; therapeutical approach and prevention.

9. **References**

The Pathogenesis of the Diabetic Foot Ulcer: Prevention and Management


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Over the last decade, it is becoming increasingly clear that diabetes mellitus is a global epidemic. The influence of diabetes is most readily apparent in its manifestation in foot complications across cultures and continents. In this unique collaboration of global specialists, we examine the explosion of foot disease in locations that must quickly grapple with both mobilizing medical expertise and shaping public policy to best prevent and treat these serious complications. In other areas of the world where diabetic foot complications have unfortunately been all too common, diagnostic testing and advanced treatments have been developed in response. The bulk of this book is devoted to examining the newest developments in basic and clinical research on the diabetic foot. It is hoped that as our understanding of the pathophysiologic process expands, the devastating impact of diabetic foot complications can be minimized on a global scale.

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