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Review Article

Diabetic foot and lower limb amputations at tertiary hospitals underscore the need for organised foot health services at primary healthcare level

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ABSTRACT

An epidemiological link between diabetes and early mortality has been reported in literature with the cause of death being mainly ischaemic heart diseases. However, a diabetic foot is a common and serious complication of diabetes with a lifetime risk of developing a foot ulcer estimated at 15-25%. Therefore, local (foot disease) and systemic (cardiovascular disease) issues should be attended to in the management of diabetes, and this emphasizes the need for a multidisciplinary team approach. A diabetic foot is defined as worsening sepsis, ulcerations, necrosis or destruction of tissues of the foot in a diabetic patient due to a complex interaction of disorders in the immune function, in the nervous and vascular systems. An improved clinical outcome is associated with wound adjunctive treatments in complementing the standard management protocol which embodies the TIME principles (tissue debridement, infection control, adequate moisture balance to promote tissue granulation in the wound bed and edges of the wound should be free from undermining).

Keywords: Diabetic foot, Adjunctive, TIME principles, Mortality, Diabetes, Sepsis, Amputation

INTRODUCTION

A strong epidemiological association between diabetes and early death has been established in literature. This is compounded by a diabetic foot ulcer (DFU) which carries an even greater risk of mortality compared to non-ulcerated diabetes. However, the number one cause of death in this population group is cardiovascular diseases, particularly ischaemic heart diseases.[1] Therefore, local (foot disease) and systemic (cardiovascular disease) factors should be addressed in the management of diabetes, and this emphasizes the need for a multidisciplinary team which includes physicians, surgeons, allied health professionals and the nursing team, amongst others.[2]

The quality of life is greatly affected by a chronic wound as seen in diabetes. Chronic wounds exude an offensive odour, may constantly be discharging pus or other serous fluids, and cause persistent foot pains. The loss of mobility leads to the inability to perform activities of daily living and to engage in pleasurable activities. Longstanding ulcers may secondarily be infected causing septicaemia, and fluid and electrolyte disturbances. The above issues add up to a feeble and unwell patient, and

directly impact on the social and mental wellbeing of the patient.[3]

A DFU is a much common and serious complication of diabetes.[4] The lifetime risk of developing a foot ulcer in diabetic patients is estimated at 15-25 %.[4] Diabetic foot sepsis (infection) is the presence of two clinical signs or symptoms of infection in or around a DFU which may include purulence, erythema, pain, swelling, warmth and indurations.[5] A diabetic foot leads to substantial morbidity, frequent visits to healthcare centres, and often results in amputation of the lower extremity/ even death.[2]

PATHOPHYSIOLOGY

A diabetic foot is characterised by worsening sepsis, deepening ulcerations, necrosis or destruction of tissues of the foot in a diabetic patient due to a complex interplay between immunopathy, neuropathy and vasculopathy.[5,6]

Immunopathy

Patients with diabetes suffer from a compromised immune system with disturbances in both humoral and cellular innate immunity. As a result, mild indolent infections can quickly turn fatal. Deficiencies in complement factor 4 and cytokine response after stimulation (humoral innate immunity) have been documented in diabetic patients. Hyperglycaemia can lead to an impairment of polymorphonuclear cell functions (cellular innate immunity), such as chemotaxis, adherence, phagocytosis and intracellular killing. High blood glucose is a good medium for the proliferation of micro-organisms, such as *Staphylococcus aureus* and β-haemolytic *Streptococci*.[7]

Neuropathy

Again, hyperglycemia leads to increased levels of intracellular glucose in the neurons and as a result the usual glycolytic pathway becomes saturated. The excess glucose gets shunted into the polyol pathway and is converted into sorbitol by aldose reductase and then fructose by sorbitol dehydrogenase. The build-up of sorbitol deranges normal action potential propagation by adversely interfering with Na^+ K^+ ATPase activity and axonal transport mechanism and causing structural breakdown of the nerves due to increased osmotic stress on their cell membranes.[8]

Peripheral neuropathy is the most common complication of diabetes and is strongly linked to poor glycaemic control and long duration of the disease.[9] Sensory polyneuropathy manifests as glove stocking pattern of distribution, in which the distal ends of extremities are first to be affected.[9] Loss of protective sensation in the feet to pain, pressure and heat predispose the patient to unnoticed trauma and subsequent tissue injury.[9] Autonomic neuropathy affects the patient's ability to sweat, and thus skin becomes dry and cracks.[9] These cracks become a portal of entry for bacteria which cause infections.[9] Motor neuropathy in diabetes plays a vital role in the initiation of Charcot's joint disease, drop-foot deformity (due to weakness of anterior compartment muscles) and supination deformity (as a result of weakness in the pronator muscles).[10,11] Weakness of intrinsic muscles of the foot upsets a delicate balance between flexors and extensors of the toes, thus causing 'hammer' toes, 'claw' toes and pes cavus.[10,11] This may lead to significant functional impairment, gait deformities and even provoke ulcer formation.[10,11]

Angiopathy

About 50% of diabetic patients have underlying peripheral arterial disease (PAD). This is usaully of a special type as it involves mainly small and medium sized arteries, often bilateral and distal with a high recurrence rate after revascularisation. PAD causes distal tissue hypoperfusion, which in turn causes distal tissue hypoperfusion, which in turn causes poor wound healing, sepsis, ulceration, digital necrosis and gangrene. This is mainly attributed to changes occurring at a cellular level. Endothelial cell dysfunction causes a decline in the release of vasodilators, such as nitric oxide, while increasing plasma thromboxane A2 production which leads to vasoconstriction and increased plasma viscosity. These patients often present with leg pains at rest, pulselessness, coldness to touch and tissue loss.[12]

ROLE OF INFECTION

Diabetic foot sepsis is a frequent and serious complication of a DFU. About 50% of DFU occur with associated infection upon presentation (Figure 1 and 2). Diabetic foot sepsis often causes multiple hospitalizations and increased exposure to numerous courses of antibiotics, and with subsequent bacterial resistance. Wound infections significantly slow the healing process and can as well lead to systemic sepsis (septicaemia). Various aspects of wound biology lead to diabetic foot sepsis, and these include the microbial load, diversity of microorganisms, the presence of infective or virulent species, and synergism between different microbial species.[7]

The infecting organisms in DFU vary considerably between regions and institutions. One study in Thailand showed that the most common organisms in DFU were Gram negative, Gram positive and polymicrobial, respectively. While a 2010 study done in Singapore revealed that Gram positive organisms were the most dominant isolates. Sasikumar et al demonstrated that septic diabetic foot patients with fever at the time of admission and a high Wagner's grade have a greater chance of harbouring anaerobic infections. As result, they recommended that drugs for anaerobic coverage should be included for all wounds beyond Wagner's grade 3.[5]

Figure 1: Diabetic foot sepsis (with auto-digestion of the second digit and surrounding cellulitis. Note the dry and scaly skin).

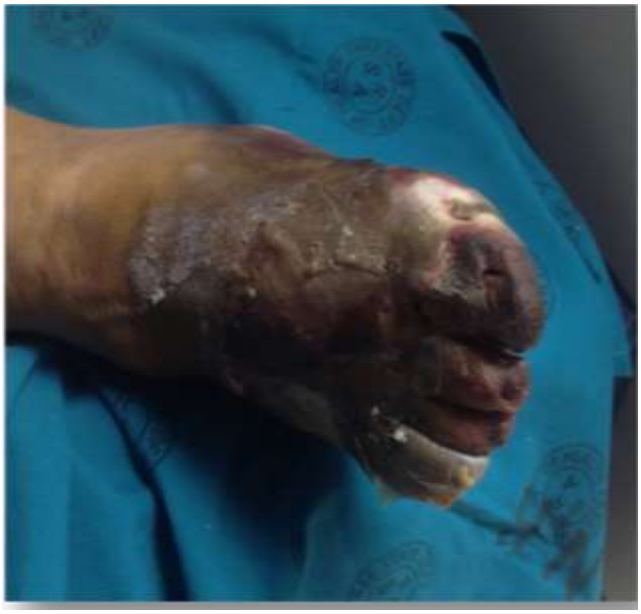

Figure 2: Diabetic foot sepsis (wet gangrene involving the entire forefoot).

Patients with mild localised infection (Wagner's grade 1 and 2) may be treated on an outpatient basis with oral agents that should cover skin flora, including *Streptococci* and *Staphylococcus aureus*.[13] Antibiotics like cephalexin, amoxicillin-clavulanate or clindamycin are usually appropriate.[13] If Gram negative organisms are implied, then double antibiotic therapy is highly recommended.[13] This is often with trimethoprim-sulfamethoxazole and amoxicillin-clavulanate (or clindamycin plus a fluoroquinolone, e.g. levofloxacin).[13] However, patients in our setting usually present late with Wagner grade 4 and 5 diabetic foot where the only definitive management is amputation and sometime coupled with revascularisation. Such patients often need fluid resuscitation, correction of electrolytes, and initial antibiotic drug treatment within the first hour according to the surviving sepsis campaign guidelines.[14] Blood cultures should be taken in order to tailor the use of antimicrobial therapy from an empiric course to more guided and culture proven drug therapy.[14]

The emergence of multidrug resistant organisms poses a challenge in the care of these patients. This mostly emanates from inappropriate use of antibiotics. It is important to note that antibiotics should not be used in wounds that have no features of infection or as prophylaxis against infection or in 'facilitating' wound healing.[7]

CLASSIFICATION

Classification of the severity of ulceration in a diabetic foot can assist in the prediction of clinical outcome. There are different types of grading systems based on parameters such as extent of infection, neuropathy, ischaemia, depth, degree of tissue loss, and location. The most widely accepted and used system is the Wagner ulcer classification system, which is primarily based on the depth of ulcer penetration, the presence of osteomyelitis, extent of tissue loss and gangrene (Table 1). The shortcomings of Wagner's classification are addressed in the university of Texas wound classification system in which two crucial parameters are assessed, i.e. wound infection and ischaemia.[15]

Table 1: Wagner grading system.[16]

Grade 0	**Intact skin**
Grade 1	**Superficial ulcer**
Grade 2	**Deep ulcer**
Grade 3	**Ulcer with the bone involvement**
Grade 4	**Forefoot gangrene**
Grade 5	**Full-foot gangrene**

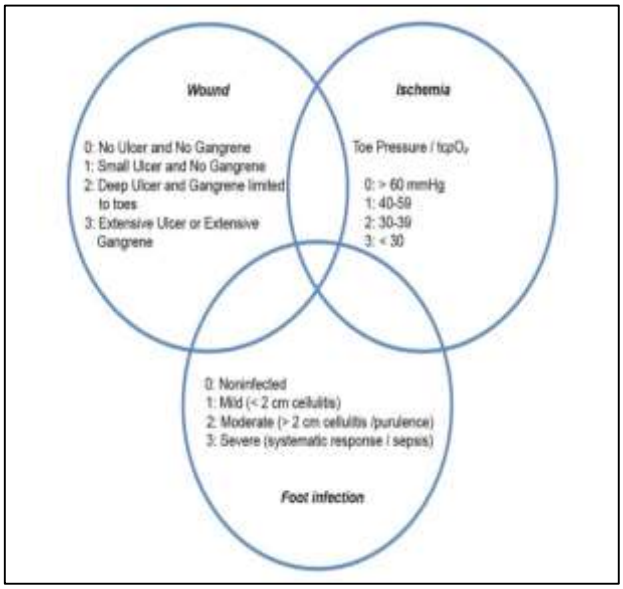

Figure 3: WIFI (wound, ischaemia, foot infection) classification.[17]

The university of Texas system is generally predictive of outcome as its increasing grades and stages are associated with poor wound healing and a greater likelihood for the need for revascularisation or amputation (Table 2).[15] Other classification systems include WIFI (wound, ischaemia and foot infection by the society of vascular surgery) (Figure 3), PEDIS (perfusion, extend, depth, infection and sensation), IDSA (Infectious Diseases Society of America), and SEWSS (Saint Elian wound score system which combines scores from the different elements of diabetic foot characteristics, such as anatomy, ischaemia, infection, neuropathy, oedema and tissue involvement).[7]

Table 2: University of Texas classification.[16]

Stage	Grade			
	0	**1**	**2**	**3**
A (no infection or ischaemia)	Pre- or post-ulcerative lesion completely epithelialised	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischaemia	Ischaemia	Ischaemia	Ischaemia
D	Both infection and ischaemia	Both infection and ischaemia	Both infection and ischaemia	Both infection and ischaemia

MANAGEMENT STRATEGIES

A diabetic foot often leads to partial or whole foot or limb amputation and, in severe cases, results in death from systemic complications of sepsis. It requires a broader attention to both local (foot) and systemic (metabolic) factors as well as a coordinated approach to its management which should include a multidisciplinary team encompassing (but not limited to) physicians, surgeons, podiatrists, dieticians, physical therapist, wound care practitioners/infectious disease specialists.[2] Personal awareness on strict glucose control, proper nutrition, regular exercise, and good foot hygiene remains pivotal in controlling diabetes and its associated complications, including a diabetic foot. Below are some of the management strategies.

Debridement

Debridement is the removal of microbial biofilm and dead tissues from a wound and it forms a critical step in expediting wound healing.[7] Surgical debridement allows proper inspection of the wound under controlled setting in theatre and the patient being free from pain. At this time, specimen for microscopy, culture and sensitivity may be taken and dressings applied.

In the clinic setting active and autolytic types of debridement can be used. Active debridement involves the physical removal of necrotic material by manual techniques, such as surgically removing necrotic tissues using a scalpel. Hydro-surgical debridement involves removing dead tissue using a strong jet of water. Autolytic debridement is done by encouraging moistening of the wound so as to facilitate natural shedding of tissue, which is mainly achieved by application hydrocolloids and hydrogels.[7]

Dressings

Wound dressings play an important role in protecting the area from bacterial invasion and environmental exposure. They promote moisture formation which facilitates new tissue generation and autolytic debridement. Some of the available dressings include acrylics, hydrocolloids, calcium alginates, hydrofibres and foams. As general rule, wounds that are highly exudative require absorbent dressings while dry wounds need moisture balance dressings.[7]

Topical antimicrobials

Topical wound antimicrobials are often discouraged due to them causing contact dermatitis and their lack of autolytic debriding ability.[7] Below are some of the preferred ones based on their low toxicity to host tissue.

Povidone iodine 10% solution

It is a broad spectrum topical antibacterial agent that is capable of penetrating through bacterial biofilm and also facilitates wound healing. It works short term and therefore wounds should be assessed regularly. Its chronic use is never advocated for as it may lead to thyroid dysfunction from iodine exposure.[7]

Chlorhexidine

It is a broad spectrum antibacterial. However, it may damage cartilaginous tissues.[7]

Acetic acid 5%

This is a potent antibacterial against *Pseudomonas* species and other Gram-negative bacteria. Its drawback is

that it is toxic to host tissue by causing fibroblast growth inhibition.[7]

Silver compounds

These agents (including silver sulphadiazine) are effective against *E. coli, Klebsiella, S. aureus* and methicillin-resistant *S. aureus* (MRSA), and they may even possess activity against fungal and viral organisms. However, they are known to be toxic to the re-epithelialization process, thus causing delayed healing.[7]

Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is an antiseptic liquid that disintegrates on contact with water and oxygen when it combines with organic tissue or blood. Hydrogen peroxide produces effervescence as it breaks down, and this aids in mechanically cleaning wounds and in the removal of tissue debris. However, its bactericidal effects are outweighed by adverse effects during prolonged topical application on wounds, and these include toxicity to epithelial cells and fibroblasts with bullae formation, skin irritation and delayed wound healing.[7]

Systemic antibiotic treatment

Systemic antibiotics are indicated when there is evidence of locally progressing or systemic infection. The type of antibiotic, route of administration and the duration of treatment are determined by culture and sensitivity studies, severity of clinical features, organ involved and immunological status of the patient. Broad spectrum antibiotics are often used before microbiological results on culture and sensitivity studies are known. Hospitalization and intravenous antibacterials are indicated in the cases of severe, non-responsive, or rapidly advancing infection.[9]

Amputation

Lower limb amputation remains a painful reality in an advanced diabetic foot infection in which it is the only option left for septic source control. In such a case it is a matter of life over limb where preservation of a highly septic necrotic foot or even leg poses a threat to life by causing overwhelming septic infection (septicemia). Early recognition and management of risk factors for DFU may prevent amputations and associated adverse outcomes. An estimated 10% of amputees will die during the admission period post lower limb amputation. Again, amputation is associated with poorer quality of life and a higher likelihood of depression which may affect psychosocial functioning. The long-term outcome after diabetic foot associated lower limb amputation is grave as 3-year survival rate stands at 35-50%.[18]

Adjunctive wound therapies

Numerous therapies have been proposed that differ from the mainstream standard of care of DFU. These modes of treatment can at best work to support and not replace conventional therapies. Examples include (but not limited to) dermal substitutes, skin grafts, negative pressure wound therapy, hyperbaric oxygen therapy, free tissue transfer, plant extracts and growth factors.[7]

CONCLUSION

The rising number of diabetes is associated with its increasing complications. A diabetic foot has emerged in increasing numbers during the past two decades. Due to an incoherent primary healthcare system in South Africa, more patients present with extensive necrosis and gangrene of the feet in which amputation remains the only option to save life over limb. The understanding of basic pathophysiology and key principles of management by health care workers would be one step in formulating a solution to this global crisis. While literature demonstrates improved outcome associated with wound adjunctive treatments in complementing the mainstay of management which embodies the TIME principles (tissue debridement, infection control, adequate moisture balance, and edges of the wound should be free from undermining); these therapies have not been operationalised in the greater treatment protocol of diabetic foot wounds at our centre. Therefore, we hope to put these treatment modalities into practice so that we improve the quality of life of the people of Ga-Rankuwa and the surrounding areas.

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