CHAPTER II

LITERATURE REVIEW

2.1 Pathogenesis of Foot Ulceration

The etiology of diabetic foot ulcers usually has many components (Boyko et al., 1999; Frykberg et al., 2000).

A multicenter study attributed 63 percent of diabetic foot ulcers to the critical triad of peripheral sensory neuropathy, peripheral arterial occlusive disease and structural foot deformity (Reiber et al., 1999).

Many of the risk factors for foot ulcer are also predisposing factors for amputation, because ulcers are primary causes leading to amputation (Pecoraro et al., 1990; Armstrong & Lavery, 1998; Boyko et al., 1999).

Neuropathic Ulcer

The pathophysiology of diabetic foot ulceration is multifactorial, but peripheral neuropathy is thought to be responsible for most cases. Diabetic neuropathy means damage of nerve fibres in people with diabetes. How the nerves are injured is not entirely clear but research suggests that high blood glucose changes the metabolism of nerve cells and causes reduced blood flow to the nerve. There are different types of nerves in the body. These can be grouped as:

- sensory (detect sensation such as heat, cold, pain)
- motor (contract muscles to control movement)

- autonomic (regulate functions one cannot control directly, such as heart rate and digestion)

Distal symmetric polyneuropathy is perhaps the most common complication affecting the lower extremities of patients with diabetes mellitus. This complication occurs in up to 58 percent of patients with longstanding disease (Harati, 1994). Neuropathy, a major etiologic component of most diabetic ulcerations, is present in more than 82 percent of diabetic patients with foot wounds (Pecoraro et al., 1990). This lack of protective sensation, combined with unaccommodated foot deformities, exposes patients to undue sudden or repetitive stress that leads to eventual ulcer formation with a risk of infection and possible amputation (Brand, 1991).

In the diabetic feet, autonomic neuropathy has several common manifestations. First, denervation of dermal structures leads to decreased sweating. This causes dry skin and fissure formation, which predispose the skin to infection. In vascularly competent patients, this "autosympathectomy" may lead to increased blood flow, which has been implicated as one of the primary etiologic factors in the development of Charcot's joint and severe foot deformity (Brower & Allman, 1981; Edmonds et al., 1985; Armstrong et al., 1997).

Motor neuropathy leading to small muscle wasting leads to an imbalance between flexors and extensors of the lower limb, causing clawing of toes and prominence of the metatarsal heads, thus providing appropriate conditions for ulceration (American Diabetes Association, 1999; Boulton, 1996).

These changes along with those previously mentioned lead to a cascade of events resulting in changes to the foot itself. According to Boultonet et al. (2004), the "triad of neuropathy, deformity and trauma is present in almost two thirds of patients

with foot ulcers." The structural changes discussed along with vascular insufficiency, infection and pressure predispose the person with diabetes (PWD) to develop foot ulceration (Figure 1).

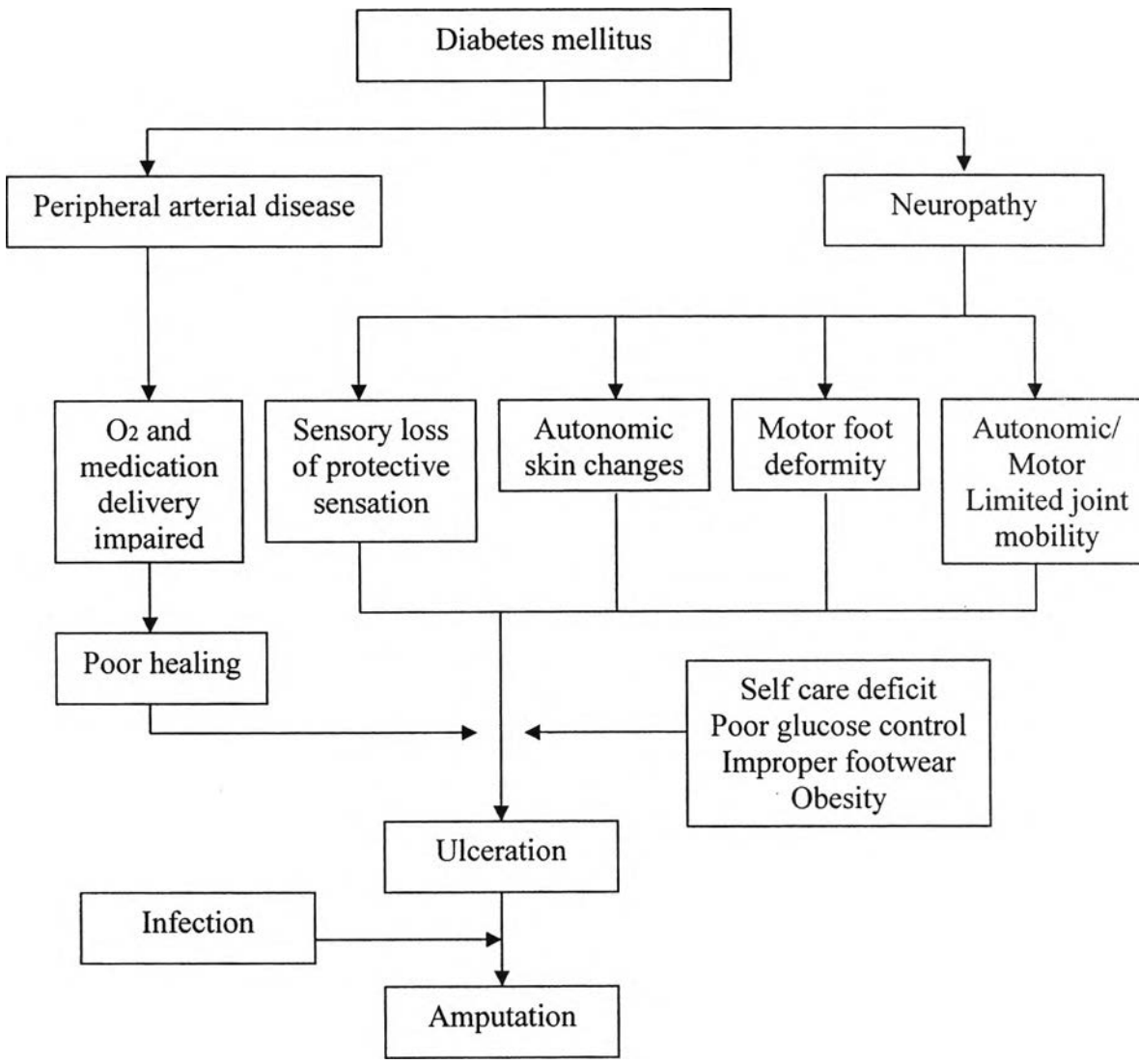

Figure 2: Pathway to Diabetic Foot Ulcer

Rarer conditions responsible for neuropathic ulcers include chronic alcoholism with malnutrition, leprosy, tabes dorsalis, spina bifida, and syringomyelia (Goldstein et al., 1998).

Peripheral Arterial Occlusive Disease

Peripheral arterial occlusive disease is four times more prevalent in diabetics than in nondiabetics (Kannel & McGee, 1979). The arterial occlusion typically involves the tibial and peroneal arteries but spares the dorsalis pedis artery (LoGerfo & Coffman, 1984). Smoking, hypertension and hyperlipidemia commonly contribute to the increased prevalence of peripheral arterial occlusive disease in diabetics (Kannel & McGee, 1985; Lee et al., 1993).

The presence of lower extremity ischemia is suggested by a combination of clinical signs and symptoms plus abnormal results on noninvasive vascular tests. Signs and symptoms may include claudication, pain occurring in the arch or forefoot at rest or during the night, absent popliteal or posterior tibial pulses, thinned or shiny skin, absence of hair on the lower leg and foot, thickened nails, redness of the affected area when the legs are dependent, or "dangled," and pallor when the foot is elevated (Armstrong & Lavery, 1998).

Noninvasive vascular tests include transcutaneous oxygen measurement (Bacharach et al., 1992), the ankle-brachial index (ABI) and the absolute toe systolic pressure (Apelqvist et al., 1989; Orchard & Strandness, 1993). The ABI is a noninvasive test that can be performed easily in the office using a handheld Doppler device. A blood pressure cuff is placed on the upper arm and inflated until no brachial pulse is detected by the Doppler device. The cuff is then slowly deflated until a Doppler-detected pulse returns (the systolic pressure). This maneuver is repeated on the leg, with the cuff wrapped around the distal calf and the Doppler device placed over the dorsalis pedis or posterior tibial artery. The ankle systolic pressure divided by

the brachial systolic pressure gives the ABI (Apelqvist et al., 1989; Bacharach et al., 1992; Orchard et al., 1993).

The sensitivity and specificity of noninvasive vascular tests are a matter of some controversy. The noninvasive tests have been faulted for underestimating the severity of arterial insufficiency. If lower extremity ischemia is strongly suspected, arteriography or some other imaging study should be performed to confirm or rule out ischemia (Caputo et al., 1994).

Optimal ulcer healing requires adequate tissue perfusion. Thus, arterial insufficiency should be suspected if an ulcer fails to heal. Vascular surgery consultation and possible revascularization should be considered when clinical signs of ischemia are present in the lower extremity of a diabetic patient and the results of noninvasive vascular tests or imaging studies suggest that the patient has peripheral arterial occlusive disease (Armstrong & Lavery, 1998).

Proper control of concomitant hypertension or hyperlipidemia can help to reduce the risk of peripheral arterial occlusive disease. Smoking cessation is essential for preventing the progression of occlusive disease. The nylon monofilament test is a simply performed office test for diagnosing patients at risk for ulcers due to peripheral sensory neuropathy (Armstrong & Lavery, 1998).

Structural Deformity and Limited Joint Mobility

Foot deformities, which are common in diabetic patients, lead to focal areas of high pressure. When an abnormal focus of pressure is coupled with lack of sensation, a foot ulcer can develop. Most diabetic foot ulcers form over areas of bony prominences, especially when bunions, calluses or hammer-toe formations lead to

abnormally prominent bony points. Foot deformities are believed to be more common in diabetic patients due to atrophy of the intrinsic musculature responsible for stabilizing the toes (Brand, 1991).

Rigid deformities or limited range of motion at the subtalar or metatarsophalangeal joints have also been associated with the development of diabetic foot ulcers. Other mechanisms of skin breakdown in the insensate diabetic foot include puncture wounds and thermal injuries from, for example, hot water soaks (Rosenbloom et al., 1981; Fernando et al., 1991).

2.2 Ulcer Evaluation

Despite the best intentions and careful attention to foot care, many diabetic patients eventually develop foot ulcers. These wounds are the principal portal of entry for infection in patients with diabetes. Frequently, the ulcers are covered by callus or fibrotic tissue. This makes the trimming of hyperkeratotic tissue important for comprehensive wound evaluation (Armstrong & Lavery, 1998).

Because these ulcers almost always form in patients with neuropathy, they are typically painless. Even in the presence of severe infection, many patients have few subjective complaints and are often more concerned with soiled footwear and stockings than with the penetrating wound (Lavery et al., 1996).

A thorough evaluation of any ulcer is critical and should direct management (Frykberg et al., 2000). An adequate description of ulcer characteristics, such as size, depth, appearance, and location, also provides for the mapping of progress during treatment (ADA, 1999). The evaluation should determine the etiology of the ulcer and ascertain whether the lesion is neuropathic, ischemic, or neuro-ischemic. Location is

important in evaluating the cause of a neuropathic foot ulcer. Usually, plantar ulcers are the result of moderate repetitive trauma underneath a metatarsal head. Medial, lateral, and digital ulcers are often the result of pressure from shoes overlying such osseous abnormalities as bunions and hammertoes (ADA, 1999; Muha, 1999; Albrant, 2000).

In patients with ulcers on the sole of the foot, the sole should be examined for signs of ascending infection, including proximal tenderness and appearance of pus on proximal compression of the sole. Surrounding calluses are typical of neuropathic ulcerations, and sinus track formation should be explored by probing the wounds (ADA, 1999).

Determining the point at which loss of protective sensation develops, and thus the risk of injury increases, is important. The loss of protective sensation is defined as the inability to perceive testing with a 5.07 Semmes-Weinstein monofilament (SWM) standardized to deliver a 10-g force. The SWM is pressed against the skin to the point of buckling. Measurements are usually taken at each of 10 sites on the foot annually (Armstrong et al., 1998).

Inability to perceive 4 or more sites is associated with a higher risk of loss of sensation and concomitant risk of ulceration (Armstrong et al., 1998; Wunderlich et al., 1998). A simplified monofilament examination using only 4 sites per foot (total 8 sites) has been used (Smieja et al., 1999).

Other common modalities that can detect insensitivity are a standard tuning fork (128 cycles per second) and a neurologic reflex hammer (Frykberg, 2002).

After describing the dimensions and appearance of the ulcer, the physician should examine the ulcer with a blunt sterile probe. Gentle probing can detect sinus

tract formation, undermining of ulcer margins, and dissection of the ulcer into tendon sheaths, bone, or joints. A positive probe-to-bone finding has a high predictive value for osteomyelitis (Grayson et al., 1995). Failure to diagnose underlying osteomyelitis often results in failure of wound healing. The existence of odor and exudate, and the presence and extent of cellulitis must be noted (Frykberg, 1991; Saar et al., 2005; Evans & Pinzur, 2005).

Because all ulcers are contaminated, culture of noninfected wounds is generally not recommended (Lipsky et al., 1990; ADA, 2006). Polymicrobial infections predominate in severe diabetic foot infections and include a variety of aerobic gram-positive cocci, gram-negative rods, and anaerobes (Lipsky et al., 1990; Caballero & Frykberg, 1998).

Radiographs should be obtained in most patients with deep or longstanding ulcers to rule out osteomyelitis; however, radiographs are not a very sensitive indicator of acute bone infection (Lipsky, 1997; ADA, 1999, 2006). When clinical suspicion indicates osteomyelitis but radiographs are negative, additional bone or leukocyte scanning is helpful in ascertaining bone involvement. However, in the neuropathic patient, bone scans are often falsely positive because of hyperemia or Charcot's arthropathy. Leukocyte scanning or magnetic resonance imaging offers better specificity in this situation (Lipsky, 1997). Ultimately, bone biopsy is necessary to firmly establish the diagnosis of osteomyelitis (Frykberg, 2002).

Vascular status must always be assessed because ischemia portends a poor prognosis for healing without vascular intervention. The simple palpation of both pedal pulses and popliteal pulses is the most reliable indication of arterial perfusion to the foot. The absence of pedal pulses in the presence of a palpable popliteal pulse is a

classic finding in diabetic arterial disease because of the selective involvement of the tibial arteries below the knee (Caputo et al., 1994; ADA, 1999). Noninvasive Doppler studies should be used to augment the clinical examination as needed, although even with these tests, the severity of arterial insufficiency can be underestimated (Caputo et al., 1994). Vascular surgical consultation is warranted when there is significant suspicion of ischemia.

Table 1: Wagner Ulcer Classification System

Grade	Lesion
0	No open lesions; may have deformity or cellulites
1	Superfici Diabetic ulcer (partial or full thickness)
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
4	Gangrene localized to portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

Source: Adapted with permission from Wagner FW Jr. The diabetic foot, Orthopedics 1987; 10: 163-72.

Classification of ulcerations can facilitate a logical approach to treatment and aid in the prediction of outcome (Frykberg, 1998; ADA, 1999; Frykberg et al., 2000). Several wound classification systems have been created, based on parameters such as extent of infection, neuropathy, ischemia, depth or extent of tissue loss, and location. The most widely accepted classification system for diabetic foot ulcers and lesions is the Wagner ulcer classification system, which is based on the depth of penetration, the presence of osteomyelitis or gangrene, and the extent of tissue necrosis (Table 1). The

drawback of the Wagner classification system is that it does not specifically address two critically important parameters: ischemia and infection (Wagner, 1987).

The University of Texas diabetic wound classification system assesses the depth of ulcer penetration, the presence of wound infection, and the presence of clinical signs of lower-extremity ischemia (Oyibo et al., 2001). This system uses four grades of ulcer depth (0 to 3) and four stages (A to D), based on ischemia or infection, or both (Lavery et al., 1996). The University of Texas system is generally predictive of outcome, because wounds of increasing grade and stage are less likely to heal without revascularization or amputation.

2.3 Treatment

The primary goal in the treatment of diabetic foot ulcers is to obtain wound closure. Management of the foot ulcer is largely determined by its severity (grade) and vascularity, and the presence of infection (Frykberg, 1991, 1998; Frykberg et al., 2000; Tai et al., 2006). A systematic approach to treatment should be taken for all diabetic foot lesions. A multidisciplinary approach should be employed because of the multifaceted nature of foot ulcers and the numerous co-morbidities that can occur in these patients (ADA, 1999; Frykberg et al., 2000). This approach has demonstrated significant improvements in outcomes, including reduction in the incidence of major amputation (Holstein & Sorensen, 1999; Dargis et al., 1999).

Rest, elevation of the affected foot, and relief of pressure are essential components of treatment and should be initiated at first presentation. Ill-fitting footwear should be replaced with a postoperative shoe or another type of pressure-relieving footwear (Frykberg et al., 2000). Crutches or a wheelchair might also be

recommended to totally off-load pressure from the foot. Although total contact casting (TCC) is considered the optimal method of management for neuropathic ulcers, it must be reapplied weekly and requires considerable experience to avoid iatrogenic lesions (Cavanagh et al., 2000). Acceptable alternatives to TCC are removable walking braces and the "half-shoe" (Frykberg et al., 2000; Hartsell et al., 2001; Armstrong et al., 2001). A mainstay of ulcer therapy is debridement of all necrotic, callus, and fibrous tissue (Armstrong & Lavery, 1998; ADA, 1999). Unhealthy tissue must be sharply debrided back to bleeding tissue to allow full visualization of the extent of the ulcer and detect underlying abscesses or sinuses. Topical enzymes have not been proved effective for this purpose and should only be considered as adjuncts to sharp debridement. Soaking ulcers is controversial and should be avoided because the neuropathic patient can easily be scalded by hot water (ADA, 1999).

Although numerous topical medications and gels are promoted for ulcer care, relatively few have proved to be more efficacious than saline wet-to-dry dressings (Frykberg et al., 2000; ADA, 1999; Hogge et al., 2000). Topical antiseptics, such as povidone-iodine, are usually considered to be toxic to healing wounds (ADA, 1999; Frykberg, 1991). Generally, a warm, moist environment that is protected from external contamination is most conducive to wound healing. This can be provided by a number of commercially available special dressings, including semipermeable films, foams, hydrocolloids, and calcium alginate swabs (Hogge et al., 2000).

The genetically engineered platelet-derived growth factor becaplermin (Regranex gel) is approved for use on neuropathic diabetic foot ulcers and can expedite healing. Growth factors stimulate chemotaxis and mitogenesis of neutrophils,

fibroblasts, and monocytes, as well as other components that form the cellular basis of wound healing (Wieman et al., 1998).

Bioen gineered skin (Apligraf) and human dermis (Dermagraft) are new types of biologically active implants for ulcers that are derived from fibroblasts of neonatal foreskins (Hogge et al., 2000; Veves et al., 2001). These bioengineered products enhance healing by acting as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements (Frykberg, 2002).

Treatment of the underlying ischemia is critical in achieving a successful outcome, regardless of topical therapies. Vascular surgical consultation should be obtained when a patient presents with an ischemic wound and when ulcers show no sign of progress despite appropriate management. A major component of the limb salvage strategy in these patients is extreme distal arterial reconstruction to restore pulsatile flow to the foot (Caputo et al., 1994; Holstein & Sorensen, 1999). The role of isolated distal endovascular procedures in this setting has not been determined. Vasodilator drugs have not been beneficial in promoting healing of ischemic lesions (Caputo et al., 1994). Hyperbaric oxygen therapy has been used as adjunctive treatment of foot ulcers; however, support for its use is limited by the small number of carefully controlled clinical trials (Wunderlich et al., 2000).

When infection is present, aerobic and anaerobic cultures should be obtained, followed by initiation of appropriate broad-spectrum antibiotic therapy (Caputo et al., 1994; Lipsky et al., 1990; ADA, 1999). Antibiotic coverage should subsequently be tailored according to the clinical response of the patient, culture results, and sensitivity testing. Surgical drainage, deep debridement, or local partial foot

amputations are necessary adjuncts to antibiotic therapy of infections that are deep or limb-threatening (Eneroth et al., 1997; Frykberg et al., 2000).

Underlying osteomyelitis is frequently present in patients with moderate to severe infections and requires aggressive bony resection of infected bone and joints followed by four to six weeks of culture-directed antibiotic therapy (Caputo et al., 1994; Lipsky, 1997; Lipsky et al., 1990; Caballero & Frykberg, 1998). The presence of deep infection with abscess, cellulitis, gangrene, or osteomyelitis is an indication for hospitalization and prompt surgical drainage. Even in the absence of bone infection, foot-sparing reconstructive procedures might be necessary to achieve final healing of the foot ulcer, especially in areas subject to exceedingly high plantar or shoe pressures (Caputo et al., 1994; Frykberg, 1998; Frykberg et al., 2000).

2.4 Prevention

Meticulous attention to foot care and proper management of minor foot injuries are a key to preventing ulcer formation (Frykberg, 1997, 1998; Armstrong & Lavery, 1998). The best approach is to make use of a team of multidisciplinary professionals who are committed to limb salvage. Centers that have instituted teams specifically for this purpose have subsequently reported dramatic reductions in lower-extremity amputation and improved rates of primary-ulcer healing (Holstein & Sorensen, 1999; Dargis et al., 1999). Patient education has a central role in treatment and should include instruction on foot hygiene, daily inspection, proper footwear, and the necessity of prompt treatment of new lesions (Frykberg, 1997, 1998; Armstrong & Lavery, 1998).

Regular foot-care examinations, including debridement of calluses and ingrown toenails, provide an opportunity to reinforce appropriate self-care behaviors and allow for early detection of new or impending foot problems (ADA, 1999; Frykberg et al., 2000).

Therapeutic shoes with pressure-relieving insoles are an essential element of ulcer prevention and have been associated with significant reductions in their development (Frykberg, 1997; Cavanagh et al., 2000).

Elective surgery to correct structural deformities that cannot be accommodated by therapeutic footwear can be performed as needed in certain patients (Caputo et al., 1994; Catanzariti et al., 1995).

Common procedures include hammertoe repair, metatarsal osteotomies, plantar exostectomies, and Achilles tendon lengthening (Catanzariti et al., 1995; Frykberg et al., 2000). In patients with neuropathy, these procedures can be easily performed under local anesthesia.

Working in unison with a vascular surgeon, these foot-sparing reconstructive procedures can even be performed after revascularization in an ischemic patient who might otherwise have needed amputation (Caputo et al., 1994).

Daily foot inspection by the patient (or a caretaker if the patient lacks sufficient visual acuity or mobility to perform the examination) is the cornerstone of proper foot care. Gentle cleansing with soap and water, followed by the application of topical moisturizers, helps to maintain healthy skin that can better resist breakdown and injury (Armstrong & Lavery, 1998).

While many patients do well with commercially available athletic shoes and thick, absorbent socks, patients with foot deformities or special support needs may

benefit from custom shoes. Patients should be reminded to avoid hot soaks, heating pads and harsh topical agents such as hydrogen peroxide, iodine (e.g., Betadine) and astringents (e.g., witch hazel). Gentle cleansing of minor wounds and the application of a topical antibiotic to maintain a moist wound environment can help to prevent ulcer formation. In addition, the physician should inspect any minor wound that does not heal rapidly (Armstrong & Lavery, 1998).

Diabetic foot ulcers can be managed without amputation by following the principles discussed above and having a thorough understanding of the pathogenesis of these ulcers.