

# Diabetic Foot Ulceration and Amputation

Stephanie Burns<sup>1</sup> and Yih-Kuen Jan<sup>2</sup>

<sup>1</sup>*Veterans Affairs Medical Center, Department of Physical Therapy,*

<sup>2</sup>*University of Oklahoma Health Sciences Center, Department of Rehabilitation Sciences,*

*Oklahoma City, Oklahoma,*

*USA*

## 1. Introduction

The number of people with diabetes mellitus (DM) has been conservatively estimated to approximately double by 2030 to a worldwide prevalence of 4.4% at which time 366 million people will have diabetes (Wild et al., 2004). As the number of people with DM rises, so too will the burden of diabetic foot disease, particularly since the factors contributing to ulcer formation such as peripheral neuropathy and vascular disease are already present in 10% of people at the time of diagnosis (Boulton et al., 2005). The risk of an individual with DM developing a foot ulcer some time in his or her lifetime could be as high as 15% and foot ulcers are found in 12% to 25% of diabetics (Singh et al., 2005; Brem et al., 2006). Results from population and community based studies in the UK have shown a 1.3-4.8% prevalence rate of foot ulcers in persons with type 2 DM (Boulton et al., 2005). The annual incidence of foot ulceration is more than 2% among all persons with diabetes and 5% to 7.6% among diabetics with peripheral neuropathy (Abbott et al., 2002; Boulton et al., 2004).

The prevalence of diabetes-related complications such as peripheral neuropathy and foot disease will continue to increase in countries such as the United States not only as the prevalence of the disease increases but as longevity of the population with DM improves. Among people with DM, lower extremity disease is the most common source of complications and hospitalization (Boyko et al.). Ghanassia et al (2008) reported a diabetic foot ulcer recurrence rate of 60.9% and an amputation rate of 43.8% in a study of 89 hospitalized subjects (Ghanassia et al., 2008). Almost 50% of nontraumatic lower extremity amputations worldwide occur in people with DM (Global Lower Extremity Amputation Study, 2000). Amputations from complications related to DM place an individual at risk for additional amputation and have a 5 year mortality rate of 39% to 68% (Morris et al., 1998). People with diabetic foot ulcers have a lower health-related quality of life than the general population and diabetics without foot ulcers as well (Ribu et al., 2007).

## 2. Pathophysiology of diabetic foot ulceration

The pathogenesis of diabetic foot ulceration is multifactorial and the result of a complex interplay of a number of elements including peripheral neuropathy, structural deformities, elevated plantar pressures, limited joint mobility, vascular disease, and various extrinsic sources of trauma such as ill fitting shoe wear or foreign objects in shoes. The peripheral

neuropathy that occurs in DM is truly a “poly”neuropathy in that sensory, motor and autonomic fibers and function are all adversely affected. It is the sequelae of these neural dysfunctions in conjunction with extrinsic factors that produce the physiologic and structural changes that lead to ulceration. The most common causal pathway to diabetic foot ulceration involves the confluence of loss of sensation resulting in failure to detect repetitive pressure or trauma and abnormal foot structure or deformity producing sites of abnormally high pressure, usually over areas of bony prominence (Mueller et al., 1990; Brem et al., 2006; Chao and Cheing, 2009; O’Loughlin et al., 2010). Diabetic peripheral polyneuropathy is the central component as it can induce changes in foot structure and produce dryness of the skin which can lead to callus formation (van Schie, 2006; O’Loughlin et al., 2010). Callusities form on areas of elevated pressure on the plantar aspect of the foot in response to pressure amplified by restricted joint motion of the ankle and foot which is applied to dry, poorly lubricated skin resulting from autonomic dysfunction (Young et al., 1992). Loss of protective sensation permits continuation of repetitive pressure that goes undetected causing calluses to thicken into sources of tissue trauma then hemorrhage and ulcerate underneath (Murray et al., 1996). Veves et al. (1992) first demonstrated the relationship between high plantar pressures and diabetic foot ulceration in a prospective study in 1992. The relative risk of developing an ulcer in an area of high plantar pressure is 4.7 and that risk more than doubles to 11.0 at the site of a callus (Murray et al., 1996).

## 2.1 Types of diabetic foot ulcers

Diabetic foot ulcers are classified as one of 3 types based on their primary etiologies and clinical characteristics: neuropathic, neuroischemic, and ischemic. This classification is a reflection of the physiological systems adversely impacted by the chronic hyperglycemia of the disease. Hyperglycemia induces alterations in multiple metabolic pathways resulting in structural and functional changes in the microvasculature of local tissue and the peripheral nerves in cases of peripheral neuropathy (Chao and Cheing, 2009). Neuropathic ulcers appear in the absence of protective sensation as a result of peripheral sensory neuropathy but without evidence of macrovascular disease. The presence of co-morbidity, deep foot infection, and plantar or metatarsal head ulcer location have been shown to be related to minor and major amputation risk in diabetic patients without ischemia (Gershater et al., 2009). They are typically found on the plantar surfaces of the feet and make up about 40% of all diabetic foot ulcers.

Diabetic foot ulcers are considered vascular or ischemic in origin when they occur in the absence of palpable pedal pulses (posterior tibial and dorsalis pedis arteries) in conjunction with ankle brachial indices (ABIs) of less than 0.9. Infection is coincident with ischemia in 50% of patients with this type of diabetic foot ulcer (Dinh et al.; Prompers et al., 2007). This type of ulcer comprises about 10% of all diabetic foot ulcerations. As their name implies, neuroischemic ulcers share features common to both ischemic and neuropathic ulcers in that they occur in the absence of protective sensation and palpable pedal pulses. They make up the final 40% of diabetic foot ulcers. Probability of major amputation in diabetic patients with ischemic/neuroischemic ulcers has been related to the extent of peripheral vascular disease, presence of co-morbidity, multiple ulcerations and tissue loss (Gershater et al., 2009). Peripheral vascular disease is the most important factor related to outcome in these types of diabetic foot ulcers (Boulton et al., 2005; Gershater et al., 2009).

## 2.2 Diabetic polyneuropathy and ulceration

Nearly 50% of all people with DM have diabetic polyneuropathy making it one of the most common long-term complications of the disease with chronic, symmetrical, sensorimotor polyneuropathy being the most typical type (Tesfaye et al., 2010). Persons with DM and signs of peripheral neuropathy have been shown to be 4 times as likely to have plantar ulcerations as those without neuropathy (Frykberg et al., 1998). Presence of peripheral neuropathy induces a number of pathologic changes in the diabetic foot that then interact to increase susceptibility to ulceration. Sensory neuropathy can affect perception of pain, pressure, touch, temperature, and proprioception. Loss of protective sensation prevents detection of levels of injurious trauma to tissue and stimuli that would ordinarily trigger a protective response such as ill fitting footwear or a foreign object in a shoe go unperceived, often until extensive destruction has occurred. Loss of sensation has been shown to be associated with diabetic foot ulceration in a number of studies (Boyko et al., 1999; Reiber et al., 1999). Results of a prospective multicenter study point to sensory neuropathy as the most frequent component in the causal sequence to diabetic foot ulceration (Reiber et al., 1999). Proprioceptive loss leads to instability and changes in gait that can increase the potential for traumatic injury.

As polyneuropathy progresses, motor fibers are affected resulting in weakness and atrophy of the distal leg and intrinsic foot muscles (Andreassen et al., 2006). Motor neuropathy can lead to foot deformities such as claw or hammertoes, prominent metatarsal heads, or hallux valgus. Prevalence of clawing or hammering toes in persons with DM has been reported to be 32 to 46% (Holewski et al., 1989; Smith et al., 1997). Hammer toe is an important predictor of plantar pressure (Mueller et al., 2003) and claw/hammer toe deformity is associated with elevated plantar pressures at the MTHs (Bus et al., 2005). Intrinsic foot muscle weakness has long been thought to be a proximate cause of deformity in the diabetic foot (Reiber et al., 1999). The intrinsic muscles of the foot ordinarily function to balance the pull of the extrinsic flexors and extensors at the interphalangeal joints by flexing the MTP joints while extending the interphalangeal joints. Weakness of the intrinsic muscles leads to loss of this stabilizing function and ultimately hyperextension of the MTP joints and clawing of the toes. Fat pads underlying the metatarsal heads, embedded in the flexor tendons and originating from the plantar ligaments attached to the proximal phalanges, tend to migrate distally when the toes claw resulting in removal of the soft tissue cushion beneath the metatarsal heads. The prominent metatarsal heads are now exposed to abnormally high plantar pressures during walking as plantar tissue thickness has been shown to be related to peak plantar pressures (Abouaasha et al., 2001). Findings of two recent studies have raised questions about the causal relationship between muscle atrophy and deformity noting that intrinsic muscle atrophy was present before clinical peripheral neuropathy could be detected and finding no significant difference in degree of intrinsic foot muscle atrophy between matched subjects with and without claw toe deformity (Greenman et al., 2005; Bus et al., 2009).

Concomitant damage to the sympathetic fibers in peripheral neuropathy results in sudomotor dysfunction that can trigger a cascade of untoward effects in the foot beginning with atrophy of the sweat glands and progressing through anhidrosis, drying of the skin, fissuring and callus formation (Vinik et al., 2003). Excessive drying has been associated with foot ulceration (Tentolouris et al., 2009). Foot temperature increases in parallel with a reduction in sweating and this may predispose to infection (Sun et al., 2008; O'Loughlin et

al., 2010). Tentolouris et al. (2009) found sudomotor dysfunction was associated with an almost 15 times greater risk of foot ulceration and similarly Sun et al. (2008) reported the risk of plantar ulceration occurrence was 13.4 times greater in a patient group with the most sudomotor dysfunction over a 4 year follow-up period.

### **2.3 Biomechanical factors and ulceration**

Limited motion at the ankle or limited joint mobility has been associated with increased peak forefoot pressures and risk of ulceration and re-ulceration (Delbridge et al., 1988). The exact pathogenesis of limited joint mobility in DM is unclear but it is thought to be due to progressive stiffening of the collagen-containing tissues ultimately resulting in thickening of the skin with loss of joint motion (Zimny et al., 2004). Giacomozzi and colleagues demonstrated reduced ankle mobility in patients with DM with and without peripheral neuropathy suggesting another mechanism is responsible for alterations in foot-ankle biomechanics (Giacomozzi et al.). Abnormal thicknesses of plantar fascia and Achilles tendon have been measured (D'Ambrogi et al., 2005; Salsich et al., 2005).

Alterations in biomechanical properties of the diabetic foot have been proven to cause increased plantar foot pressure, which may lead to the development of diabetic foot ulcers (Mueller et al., 2003). Diabetes is associated with the formation of glucose-mediated intermolecular cross-links (i.e. advanced glycation end-products, AGE). Accumulations of AGEs increase stiffness of the cartilages, muscles, tendons, ligaments, and skin (Brownlee et al., 1988). A stiffer plantar soft tissue reduces the shock-absorbing mechanism of the ankle-foot complex and may make the diabetic foot more vulnerable to repetitive stress during walking (Landsman et al., 1995).

The hallux has been identified as the most common site of diabetic foot ulceration, accounting for 20% to 30% of diabetic foot ulcers in a study of 360 patients and comprising 22% of the ulcers seen in another research group's clinic (Armstrong et al., 1998; Nube et al., 2006). Several risk factors have been associated with ulceration of the hallux. Decreased dorsiflexion at the first metatarsophalangeal joint, neuropathy, increased length of the hallux, increased interphalangeal angle, increased body weight, decreased soft tissue thickness and pes planus are all associated with increased pressure at the hallux (Mueller et al., 2003).

Another common deformity seen in diabetic feet is Charcot's neuroarthropathy. Charcot's foot is characterized by neuropathic fractures of the midfoot region resulting in collapse of the arch of the foot. Involvement of the tarsal joints can cause the plantar surface to become convex resulting in the classic "rocker-bottom" foot. This deformity leads to areas of elevated pressure on skin that is not adapted to tolerate pressure and ultimately leads to ulceration (Mueller et al., 1990). Abnormal perfusion of the bones of the midfoot precipitated by autonomic neuropathy may be an etiologic component (O'Loughlin et al., 2010). Both Charcot deformity and hammer toes have been shown to be independent risk factors for diabetic foot ulcers (Boyko et al., 1999).

### **2.4 Microvascular factors and ulceration**

Adequate vascular supply is essential for healing and ischemia often plays a role in ulceration of the diabetic foot. Wound healing requires an adequate supply of oxygen and nutrients be provided to cells involved in the repair process. Peripheral arterial disease

(PAD) is estimated to occur twice as frequently among persons with DM as those without (Dinh et al.). Lower extremity arterial insufficiency in persons with DM can have both macro- and microvascular components. Probability of healing in diabetic foot ulcers has been shown to be strongly related to severity of peripheral vascular disease (Apelqvist et al., 2011). The reported prevalence of PAD in patients with diabetic foot ulcers ranges from 10% to 60% (Armstrong and Lavery, 1998; Oyibo et al., 2001; Moulik et al., 2003). A multi-center trial in Europe reported an overall PAD prevalence of 49% but this varied from 22 to 73% among various centers (Prompers et al., 2007). Peripheral arterial disease typically affects infrapopliteal vessels specifically the profunda femoris in people with DM (Dinh et al.).

Tissue viability ultimately depends on adequate local blood supply to cells via the microcirculation. Alterations in microcirculation have been implicated in formation of diabetic foot ulcers for some time (Dinh and Veves). Dysfunction in the microcirculation of the diabetic foot is not occlusive in nature but secondary to structural and functional changes (Dinh et al.; Chao and Cheing, 2009). The chronic hyperglycemia brought on by DM leads to intracellular accumulation of glucose inducing alterations in multiple metabolic pathways in vascular and neural tissue. Hyperglycemia is a causative factor in impaired vascular permeability and tone as well as auto regulation of blood flow (Chao and Cheing, 2009). Impaired vasodilatory response to plantar pressure causing tissue ischemia is the common final pathway, according to various theories, of the development of diabetic foot ulcers (Boulton et al., 2000). Diabetic patients (with or without peripheral neuropathy) suffer from various forms of microvascular dysfunction, including abnormal vasomotion (Benbow et al., 1995; Stansberry et al., 1996; Bernardi et al., 1997), impaired vasodilatory response to local heating (Malik et al., 1993; Stansberry et al., 1999), decreased blood flow under or after pressure loading (Fromy et al., 2002; Koitka et al., 2004), endothelial nitric oxide dysfunction (Veves et al., 1998), and attenuated response to sympathetic maneuvers (Aso et al., 1997).

Thickening of basement membranes and reduction in capillary size are structural changes that are more prominent in the lower extremities (Dinh et al.). Functionally, vasoreactivity is impaired via reduction in both endothelium-dependent and non-endothelium dependent vasodilation. Both endothelium- and non-endothelium-dependent vasodilation are impaired in the presence of peripheral neuropathy while PAD primarily affects non-endothelium-dependent vasodilation (Dinh et al.; Veves and King, 2001). Occlusive vascular lesions would be more amenable to surgical intervention while the functional ischemia resulting from dysfunctional vasoreactivity would be less responsive to bypass procedures (Veves et al., 1998). Therefore correction of macrocirculatory issues will not necessarily result in healing of a diabetic foot ulcer or prevention of one in the future (Arora et al., 2002).

Microcirculation in persons with DM can also be adversely affected by the neuropathic impairment of the nerve-axon reflex. Stimulation of the C-nociceptive nerve fibers ordinarily leads to release of local vasodilators such as substance P, bradykinin and calcitonin gene-related peptide (CGRP). These neuropeptides act to produce vasodilation via direct action on vascular smooth muscle or indirectly on mast cells through histamine release. This axon mediated response normally accounts for roughly 1/3 of the endothelium-dependent vasodilation in the foot and forearm (Hamdy et al., 2001). This neurogenic vasodilatory response is impaired in the presence of diabetic peripheral neuropathy and the number of sensory neurons for substance P and CGRP reduced (Levy et al.; Caselli et al., 2003).

## 2.5 Diabetic foot ulcers and lower extremity amputation

DM increases the risk for lower extremity amputation (LEA) from 2% to 16% depending on study design and the population studied (Adler et al., 1999; Lavery et al., 2003; Resnick et al., 2004; Frykberg et al., 2006). Rates of LEA among persons with DM can be as much as 15 to 40 times higher than their non-DM counterparts (Lavery et al., 1996; Resnick et al., 1999). Incidence rates of all LEAs are 4-7 times higher in men and women with DM than in people without DM (Frykberg et al., 2006). A Dutch study found the incidence rate of initial unilateral LEA was 8 times higher in persons with DM than in persons without DM (Johannesson et al., 2009). Lavery et al. found men with DM were 2.35 times more likely to have an LEA than women with DM (Lavery et al., 1999). In a Native American population with DM, risk of LEA was twice as high for men as women (Resnick et al., 2004). Amputation risk varies among ethnic groups being 1.72 to 2.17 times higher in African Americans than non-Hispanic whites and Hispanics (Lavery et al., 1996) and Native Americans, Hispanic Americans and African Americans having a 1.5 to 2.4 fold increased risk of DM-related LEAs than their age-matched Caucasian counterparts (Lavery et al., 1999; Resnick et al., 2004).

The majority of LEAs due to DM were toe amputations followed by BKAs then AKAs and foot amputations with rates of 2.6, 1.6, and 0.8 per 1000 in 2002 (Centers for Disease Control and Prevention, 2005). Several studies in the US and western Europe in recent years have reported decreasing incidence of LEAs in DM populations particularly in response to implementation of improved diabetes foot care (Krishnan et al., 2008; Schofield et al., 2009). In the 5 year longitudinal study by Canavan et al. (2008), the incidence rate of LEA in persons with DM dropped from 310.5 per 100,000 persons to 75.9 per 100,000. A similar dramatic 62% reduction in incidence of major LEAs and a more modest 40.3% decline in total LEAs over 11 years were reported (Krishnan et al., 2008). However, a large retrospective study utilizing a nationwide sample in England found no significant decrease in incidence of DM-related LEAs from 2004 to 2008 (Vamos et al., 2010). The explanation for the differences in findings may lie in the differences in study design as retrospective studies have been reported to underestimate incidence by 4.2% to 90.6% and misclassify 4.5% to 17.4% of amputations (Rayman et al., 2004).

## 2.6 Risk factors for diabetes-related amputation

Generally speaking, the same factors involved in ulceration of the diabetic foot can have at least contributory roles in LEAs. PAD, infection, chronic hyperglycemia, and history of previous diabetic foot ulcers or amputation are significant risk factors for amputation. Ischemia is a contributory if not the major factor determining the need for a LEA (Schofield et al., 2006). PAD is an independent risk factor for LEA in people with DM (Adler et al., 1999; Moulik et al., 2003; Davis et al., 2006). Adequate blood supply is necessary for healing and resolution of infection as impaired blood interferes with tissue oxygenation and antibiotic delivery to affected regions. PAD is present in 8% of adults with DM at the time of diagnosis and there is a 3.5 fold risk among men with DM and a 8.6 fold risk among women of developing PAD (Melton et al., 1980; Kannel, 1985). In a study by Moulik et al. (2003), 59% of patients who had LEAs over a 5 year follow-up period had PAD and 5 year amputation rates were higher and times to amputation were shorter in this group. While infection may not be an independent risk factor for LEA is often related to inadequate blood flow and interferes with healing (Reiber et al., 1999).

Chronic hyperglycemia and insulin use, which could be considered a marker for glycemic control, have been shown to be independent risk factors for LEA in persons with DM (Adler et al., 1999; Davis et al., 2006; Adler et al., 2010). Elevated HbA1c is associated with risk of LEA such that for every 1% increase in HbA1c there is an associated 26% to 36% increased risk of LEA (Adler et al., 2010). Positive associations have been observed between glycemia and micro- and macrovascular complications and clinical trials have demonstrated the value of improved glycemic control on microvascular complications (DCCT, 1993; UKPDS, 1998). Data on macrovascular complications and glycemic control is less clear with limited clinical trial data to unequivocally demonstrate that intensive glycemic control reduces risk of LEA (Zoungas et al., 2008; Patel et al., 2009; Adler et al., 2010).

Increased risk of LEA associated with hyperglycemia is thought to be mediated by PAD and peripheral sensory neuropathy. Various biochemical changes resulting from hyperglycemia including glycation, protein kinase C activation, sorbitol and hexosamine pathway activation result in arterial disease, sensory neuropathy, autonomic dysfunction and ultimately deregulation of blood flow (Adler et al., 2010). History of diabetic foot ulcers and previous amputation are both independent predictors of LEAs (Adler et al., 1999; Resnick et al., 2004; Davis et al., 2006). Presence of a diabetic foot ulcer is the single biggest risk factor for nontraumatic amputation in persons with DM and increases the risk of amputation 6-fold (Brem et al., 2006; Davis et al., 2006). A diabetic foot ulcer precedes 85% of major LEAs in individuals with DM (Larsson et al., 1997). The presence of a diabetic foot ulcer alone in a person with DM increases the risk of LEA 7 times relative to patients with Charcot arthropathy alone and diabetic foot ulcers together with Charcot arthropathy increases the risk of LEA 12 times versus Charcot arthropathy alone (Sohn et al., 2010).

## **2.7 Morbidity and mortality following diabetes-related lower extremity amputation**

The causal factors leading to the initial amputation remain in place following LEA and continue to place these individuals at elevated risk for re-ulceration. Re-ulceration risk is higher in those with a previous amputation due to increased pressure on a smaller residual weight bearing area, abnormal pressure distribution on the remaining plantar surface and alterations in bony architecture. Thirty-four percent of amputees re-ulcerate in the first year and 70% after 5 years (Apelqvist et al., 1993). Further amputation is twice as likely in persons with DM than in those without with 22% undergoing another amputation a median of 7 months following initial amputation (Schofield et al., 2006). Re-amputation at a higher level on the residual limb is a function of disease progression, failure to heal, and risk factors that develop as a result of the initial amputation such as alteration in the pressure distribution on the residual weight bearing surface. Age and heel lesions have also been shown to be risk factors for re-amputation (Skoutas et al., 2009). Risk of re-amputation is highest within the first 6 months of initial amputation (Izumi et al., 2006; Skoutas et al., 2009). A re-amputation rate of 21.5% within 18 months was reported by Skoutas et al (2009) and 1 year and 3 year rates of 26.7% and 48.3% by Izumi (2006). Forty percent of subjects with DM in a study by Tentolouris et al. had an ipsilateral or contralateral amputation within an average of about 16 months of the first DM-related LEA (Tentolouris et al., 2004).

Mortality risk following LEA is higher for individuals with DM than those without DM. People with DM had a 55% increased risk of death after amputation compared to those without DM (Schofield et al., 2006). One of the first prospective studies on long-term

prognosis following LEA amputation reported 1, 3, and 5 year mortality rates of 15%, 38%, and 68%, respectively for both minor and major amputations combined (Larsson et al., 1997). Almost 10 years later, researchers were still reporting people with DM who underwent LEA had a 55% greater risk of dying than those without DM (Schofield et al., 2006).

### **3. Management of diabetic foot ulceration**

The over-arching goal of healthcare professionals engaged in the management of persons with DM is to successfully intervene in the causal pathway leading to diabetic foot ulcers and ultimately amputation. Management of the diabetic foot can be viewed in 4 phases: prevention, accommodation or adaptation, healing and rehabilitation which unfortunately often circles around to become prevention again in an effort to prevent re-ulceration. The scope of this chapter limits discussion primarily to the healing phase of this process.

Clinical trial data suggest better glycemic control mitigates the microvascular complications of the disease including peripheral neuropathy (DCCT, 1993; UKPDS, 1998). Preventing or delaying onset of peripheral neuropathy and its attendant sensory, motor, and autonomic sequelae is paramount to prevention of diabetic foot ulcers. Peripheral polyneuropathy and the tissue changes it induces: loss of protective sensation; inability to perceive trauma; structural changes leading to deformity and areas prone to excessive pressure; impaired sweat gland function producing dry, atrophic skin, all lead to a foot susceptible to injury.

Once peripheral neuropathy is present, focus of care shifts to managing and successfully adapting to the attendant tissue changes. Patient education on foot care becomes even more critical including routine foot inspection, lubrication of dry skin, avoidance of soaking feet, and appropriate callus and nail management. Adaptive footwear must be provided at frequent intervals to accommodate structural changes and relieve pressure.

#### **3.1 Treatment of diabetic foot ulcers**

Healing of DFUs is related to how well the underlying etiologies of neuropathy and ischemia and their consequences are addressed. Traditionally, five elements are considered critical to adequate treatment of diabetic foot disease: off-loading or pressure relief, revascularization when appropriate, debridement, management of infection, and wound care. As the magnitude of diabetic foot disease has continued to grow along with our understanding of wound healing in general and the pathophysiology of DM in particular, wound care strategies have progressed as well and there are an ever growing number of advanced wound care products and therapies available. Some of the more widely available include preventive surgery, negative pressure wound therapy (NPWT), hyperbaric oxygen therapy (HBO), and advanced wound care products such as growth factors and living skin equivalents.

#### **3.2 Off-loading**

Diabetic foot ulcers on weight or pressure bearing areas in feet lacking protective sensation must be unloaded or relieved of pressure to facilitate healing. A recent review of off-loading techniques for the diabetic foot by Cavenagh and Bus (2011) notes total contact casting

(TCC) remains the gold standard for off-loading although removable walkers have also been shown to provide a similar degree of pressure relief. Peak pressure reduction in the forefoot is reported to be up to 87% with TCC but only 44% to 64% with cast shoes and forefoot offloading shoes (Cavanagh and Bus, 2011). Rocker bottom outsoles, custom insoles, metatarsal pads and arch supports may reduce forefoot peak pressure 16% to 52% compared to controls (Cavanagh and Bus, 2011).

Effectiveness of an off-loading device must be gauged by both its ability to relieve pressure and patients' adherence to the treatment. TCCs are considered to be effective in part because they essentially coerce patient adherence to treatment. Some of the unloading is achieved by restricting ankle motion and redistributing load to the device itself which may explain why devices that extend only to the ankle are less effective in off-loading the foot than those that reach above the ankle (Cavanagh and Bus, 2011). The majority of evidence for off-loading comes from studies examining uncomplicated neuropathic plantar ulcers. TCC has been shown to be more effective in time to healing than removable devices in some randomized clinical trials while a recent RCT showed similar healing rates between a TCC and an ankle high removable walker (Faglia et al., 2010). Off-loading has been used to treat neuroischemic or infected wounds but success rates are much lower than for purely neuropathic ulcers (Nabuurs-Franssen et al., 2005). TCCs are not in wider use because of potential adverse reactions which include diminished activity level, problems sleeping or driving a car and iatrogenic ulcers from poorly applied casts.

Cavanagh and Bus (2011) summarized the recommendations of the International Working Group on the Diabetic Foot for use of off-loading in management of non-complicated foot ulcers in their review: 1) pressure relief should be part of every treatment plan; 2) TCC and non-removable walkers are preferred but clinicians should be aware of potential adverse effects; 3) forefoot off-loading shoes or cast shoes may be used when the above devices are contraindicated or not tolerated; and 4) conventional or standard footwear should not be used as other devices are more effective.

### 3.3 Revascularization

Peripheral vascular disease is common in persons with DM and is characterized by impairment at both macro- and microvascular levels. Re-establishing arterial supply is the key to healing ischemic and neuroischemic ulcers. Treatment of peripheral arterial disease involves management of risk factors, medical therapy, and endovascular or open surgery. Smoking cessation, weight loss, and adherence to a low fat diet are all areas in which eliciting patient cooperation is critical for successful management. Antiplatelet therapy, anticoagulation, and LDL lowering drugs may also play a role in treatment. However, many diabetic patients will need re-vascularization to achieve healing. Macrovascular disease is morphologically the same in diabetics and non-diabetics differing only in location with the anterior and posterior tibial and peroneal arteries of the calf being most affected in persons with DM. Surgical options are dependent on whether the vascular disease is supra-inguinal (aorto-iliac) or infra-inguinal (femoro-popliteal-crural) or both ((Ruef et al., 2004). Angioplasty, endarterectomy, grafting, and by-pass are some available surgical interventions. Vascular surgery may be able to aid in revascularization of an area via restoring flow through larger vessels but will not completely restore the microvascular flow disrupted by structural changes in the basement membranes or functional impairment in microcirculation caused by the disease.

### 3.4 Debridement

Debridement is necessary for removal of devitalized tissue in order to create a healthier wound bed. Removal of nonviable tissue permits better visualization of the wound base, removes a growth medium for bacteria and stimulates release of growth factors. Sharp debridement is the gold standard for diabetic foot ulcers and is the most efficient method for removing large amounts of tissue quickly. Other types of debridement include autolytic, enzymatic, and biologic.

### 3.5 Management of infection

All open wounds can potentially provide warm, moist environments attractive to microorganisms and thus run the risk of being colonized making infection difficult to diagnose microscopically. The diagnosis of infection is typically based on the presence of purulent drainage or at least 2 clinical signs of inflammation (warmth, erythema, induration, pain, and tenderness) but as these can be mimicked and obscured by the presence of neuropathy or ischemia; it has been proposed that friable tissue, wound undermining and foul odor be used to indicate infection (Pittet et al., 1999; Edmonds and Foster, 2004). Systemic signs of infection such as fever and leukocytosis are not typically seen with diabetic foot ulcers but when present, signal the infection is likely severe (Cavanagh et al., 2005).

As noted earlier, virtually all wounds are colonized so tissue specimens obtained via biopsy, curettage, or aspiration are preferable to wound swabs because results are more specific and sensitive (Lipsky et al., 2004). The most important pathogens implicated in DFU infections are aerobic gram-positive cocci especially *Staph. Aureus* but also  $\beta$  hemolytic streptococci and coagulase-negative staphylococci. Treatment of infection in bone underlying a diabetic foot ulcer presents a particular challenge. Osteomyelitis should be considered present if bone is visible in the wound or palpable with a probe. Bone scans and labeled white blood cell scans are more sensitive for detecting osteomyelitis than plain film x-rays but relatively non-specific and less accurate than MRI. A bone biopsy preferably obtained percutaneously or by surgical debridement is the gold standard test for osteomyelitis but carries the obvious risks associated with invasive testing.

### 3.6 Wound care

In one sense, care of a wound on a diabetic foot is no different from the care of any other wound in that the basic tenets of wound care apply. A healthy wound environment must be created by removing necrotic tissue, managing bacterial load and maintaining an appropriate moisture balance. Effective use of wound dressings provides a wound environment that encourages angiogenesis, prevents tissue dehydration, promotes cell migration and interaction of growth factors with target cells (Field, 1994). Wound care products are available in a dazzling array to address all aspects of wound bed management but there are unfortunately few RCTs available to support clinical effectiveness. However, it is important to note that local wound care is insufficient for healing of diabetic foot ulcers in most cases unless the underlying diabetic etiologic factors are addressed.

### 3.7 Preventive surgery

Surgery may be necessary to correct biomechanical faults and/or distribute pressure in order to promote healing of a diabetic foot ulcer or prevent re-ulceration. Prophylactic surgery to correct deformities prior to ulceration has been advocated as a preventive strategy (Mueller et al., 2003). Ulcer healing can be accelerated and recurrence prevented in feet with toe deformities by utilization of extensor tenotomy (Margolis et al., 2005). Achilles tendon lengthening reduces pressure under the metatarsal heads and promotes ulcer healing but the concomitant gait alteration increases the risk of heel ulcers prompting these authors to recommend avoiding this procedure in individuals with complete sensory loss of the heel pad (Holstein et al., 2004). Metatarsal osteotomy and metatarsal head resection have been advocated by some but these procedures pose the risk of secondary ulceration or Charcot foot formation (Petrov et al., 1996; Fleischli et al., 1999). RCTs comparing surgical and non-surgical management of DFUs are scarce. Finally, any surgery is producing a wound that carries a risk of non-healing and infection.

### 3.8 Negative pressure wound therapy

Negative pressure wound therapy utilizes a vacuum pump to create a subatmospheric wound environment. A wound dressing, typically an open cell foam or saline moistened gauze is placed in the wound cavity to distribute the pressure. A tube connects the cavity to the vacuum pump and the area is sealed with an adhesive film. The portable vacuum pump exerts and maintains a negative pressure in the range of about 50 to 125 mmHg. The mechanical force exerted by the vacuum on the wound surface creates microstrain induced microdeformations of the wound tissue which in turn promotes cellular stretch and proliferation. Micromechanical forces resulting from the negative pressure encourage cell proliferation and migration, extracellular matrix deposition and gene expression. The subatmospheric pressure also prompts angiogenesis and reduction in local edema, excess interstitial fluid, increased lymphatic flow, and removal of waste by-products (Krasner Diane L; Rodeheaver, 2007). Authors of an RCT examining the effectiveness of NPWT in DFUs reported the incidence of secondary amputation was significantly lower when using NPWT (4.1%) compared to moist wound care (10.2%) (Blume et al., 2008). Increased granulation tissue formation and decreased healing times were seen in a RCT of 162 diabetic subjects with partial foot amputations (Armstrong et al., 2005).

### 3.9 Hyperbaric oxygen therapy

Recognizing that a fundamental problem in non-healing wounds was hypoxia; researchers sought ways to raise tissue oxygen levels. Hyperbaric oxygen therapy entails breathing 100% oxygen pressurized typically between 2.0 and 2.5 absolute atmospheres or ATAs (1 ATA = atmospheric pressure at sea level) with the goal of raising the oxygen partial pressure to about 1500 mmHg. Oxygen delivery to the wound is subsequently improved by the HBO-provided increase in blood oxygen concentration. In addition, HBO has been shown stimulate angiogenesis, enhance neutrophil killing ability, and stimulate fibroblast activity and collagen synthesis (Hunt and Pai, 1972; Knighton et al., 1986). A number of RCTs supporting the efficacy of HBO in the treatment of DFUs have been published but there are still questions about its therapeutic benefits (Tecilazich et al., 2011) and its non-selective use among persons with diabetic foot ulcers (Londahl et al., 2011).

### 3.10 Advanced wound care products

Wound healing is regulated at least in part by the action of growth factors at various points in the healing cascade. Growth factors are polypeptides transiently produced by cells that exert hormone-like effects on other cells by binding to surface receptors and activating cellular proliferation and differentiation. Some of the more important growth factors for healing include platelet-derived growth factor, transforming growth factor alpha and beta, fibroblast growth factor and epithelial growth factor. Many growth factors are decreased in chronic diabetic foot ulcers. An example of a topically applied growth factor is the genetically engineered, recombinant DNA platelet-derived growth factor, becaplermin. Becaplermin addresses the lack of platelet-derived growth factor-BB and stimulates chemotaxis and mitogenesis of neutrophils, fibroblasts and monocytes. On a cautionary note, the FDA issued a black box warning for this product citing increased risk of death from cancer in patients who used 3 or more tubes of the product.

Living skin equivalents (LSE) comprise another class of advanced local wound care products that is rapidly expanding. These tissue-engineered skins offer notable advantages over skin grafting: because their use is non-invasive, anesthesia is not required, they can be applied in out-patient settings and potential donor site complications such as infection and scarring are avoided. Bioengineered tissue acts not only as a biological dressing but also facilitates healing by filling the wound with extracellular matrix and inducing the expression of growth factors and cytokines which in turn facilitate the healing cascade. LSEs are available for epidermal, dermal and composite (dermal and epidermal) wounds. Autologous grafts or autografts are comprised of cells harvested from the patient then cultured. Grafts from these master cell cultures can then be subcultured into sheets and obtained from an unrelated donor. Allergenic grafts are tissue engineered from neonatal fibroblasts and keratinocytes.

## 4. Conclusion

The complexity and multifaceted nature of diabetic foot ulceration requires a coordinated approach by a multidisciplinary team of healthcare providers yet even when optimal treatment is provided one study suggests only about 50% of diabetic foot ulcers will be healed after 12-20 weeks. Experts suggest the most cost-effective way to approach wound care in this population is through implementation of a standardized treatment regimen with assessment of wound healing rate every 4 weeks. Advanced wound care therapies should be reserved for those diabetic foot ulcers with healing rates < 50% after 4 weeks. All diabetic foot ulcers are initially managed with a standardized treatment regime and re-assessed every 4 weeks. Wounds healing at a rate of 50% or more continue with the standard regimen while those healing at a rate below 50% receive more aggressive treatment approaches. It should be emphasized that these advanced wound care therapies are in addition to the standard treatments of offloading, debridement, ischemia and infection management.

Diabetic foot ulcers and LEAs present challenges to clinicians not only as serious but ultimately preventable sources of pain, suffering and death to individuals but as virtual black holes to health care resources. A clearer understanding of the nature of these complications and the threats they pose will enable healthcare providers to make informed decisions and implement best practices of care.

## 5. Acknowledgment

This study was supported by the Oklahoma Center for the Advancement of Science and Technology (OCAST HR09-048).

## 6. References

- Abbott, C. A., A. L. Carrington, H. Ashe, S. Bath, L. C. Every, et al. (2002). "The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort." *Diabetic Medicine* 19(5): 377-384.
- Abouaeha, F., C. H. van Schie, G. D. Griffiths, R. J. Young and A. J. Boulton (2001). "Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot." *Diabetes Care* 24(7): 1270-1274.
- Adler, A., S. Erqou, T. Lima and A. Robinson (2010). "Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus—review and meta-analysis." *Diabetologia* 53(5): 840-849.
- Adler, A. I., E. J. Boyko, J. H. Ahroni and D. G. Smith (1999). "Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers." *Diabetes Care* 22(7): 1029-1035.
- Andreassen, C. S., J. Jakobsen and H. Andersen (2006). "Muscle Weakness: A Progressive Late Complication in Diabetic Distal Symmetric Polyneuropathy." *Diabetes* 55(3): 806-812.
- Apelqvist, J., T. Elgzyri, J. Larsson, M. Londahl, P. Nyberg, et al. (2011). "Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients." *Journal of Vascular Surgery* 53(6): 1582-1588.
- Apelqvist, J., J. Larsson and C. D. Agardh (1993). "Long-term prognosis for diabetic patients with foot ulcers." *Journal of Internal Medicine* 233(6): 485-491.
- Armstrong, D. G. and L. A. Lavery (1998). "Elevated peak plantar pressures in patients who have Charcot arthropathy." *Journal of Bone & Joint Surgery - American Volume* 80(3): 365-369.
- Armstrong, D. G., L. A. Lavery and C. Diabetic Foot Study (2005). "Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial." *Lancet* 366(9498): 1704-1710.
- Armstrong, D. G., L. A. Lavery and L. B. Harkless (1998). "Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation." *Diabetes Care* 21(5): 855-859.
- Arora, S., F. Pomposelli, F. W. LoGerfo and A. Veves (2002). "Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization." *Journal of Vascular Surgery* 35(3): 501-505.
- Aso, Y., T. Inukai and Y. Takemura (1997). "Evaluation of skin vasomotor reflexes in response to deep inspiration in diabetic patients by laser Doppler flowmetry. A new approach to the diagnosis of diabetic peripheral autonomic neuropathy." *Diabetes Care* 20(8): 1324-1328.
- Benbow, S. J., D. W. Pryce, K. Noblett, I. A. MacFarlane, P. S. Friedmann, et al. (1995). "Flow motion in peripheral diabetic neuropathy." *Clinical Science* 88(2): 191-196.

- Bernardi, L., M. Rossi, S. Leuzzi, E. Mevio, G. Fornasari, et al. (1997). "Reduction of 0.1 Hz microcirculatory fluctuations as evidence of sympathetic dysfunction in insulin-dependent diabetes." *Cardiovascular Research* 34(1): 185-191.
- Blume, P. A., J. Walters, W. Payne, J. Ayala and J. Lantis (2008). "Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial." *Diabetes Care* 31(4): 631-636.
- Boulton, A. J., H. Connor and P. R. Cavanagh (2000). *The Foot in Diabetes*. New York, NY, John Wiley & Sons, Inc.
- Boulton, A. J., R. S. Kirsner and L. Vileikyte (2004). "Clinical practice. Neuropathic diabetic foot ulcers. [Review] [54 refs]." *New England Journal of Medicine* 351(1): 48-55.
- Boulton, A. J. M., L. Vileikyte, G. Ragnarson-Tennvall and J. Apelqvist (2005). "The global burden of diabetic foot disease." *Lancet* 366(9498): 1719-1724.
- Boyko, E. J., J. H. Ahroni, V. Cohen, K. M. Nelson and P. J. Heagerty "Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study." *Diabetes Care* 29(6): 1202-1207.
- Boyko, E. J., J. H. Ahroni, V. Stensel, R. C. Forsberg, D. R. Davignon, et al. (1999). "A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study." *Diabetes Care* 22(7): 1036-1042.
- Brem, H., P. Sheehan, H. J. Rosenberg, J. S. Schneider and A. J. M. Boulton (2006). "Evidence-based protocol for diabetic foot ulcers." *Plastic & Reconstructive Surgery* 117(7 Suppl): 193S-209S; discussion 210S-211S.
- Brownlee, M., A. Cerami and H. Vlassara (1988). "Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications." *New England Journal of Medicine* 318(20): 1315-1321.
- Bus, S. A., M. Maas, A. L. H. De Lange, R. P. J. Michels and M. Levi (2005). "Elevated plantar pressures in neuropathic diabetic patients with claw/hammer toe deformity." *Journal of Biomechanics* 38(9): 1918-1925.
- Bus, S. A., M. Maas, R. P. Michels and M. Levi (2009). "Role of intrinsic muscle atrophy in the etiology of claw toe deformity in diabetic neuropathy may not be as straightforward as widely believed." *Diabetes Care* 32(6): 1063-1067.
- Caselli, A., J. Rich, T. Hanane, L. Uccioli and A. Veves (2003). "Role of C-nociceptive fibers in the nerve axon reflex-related vasodilation in diabetes." *Neurology* 60(2): 297-300.
- Cavanagh, P. R. and S. A. Bus (2011). "Off-loading the diabetic foot for ulcer prevention and healing." *Plastic & Reconstructive Surgery* 127: Suppl-256S.
- Cavanagh, P. R., B. A. Lipsky, A. W. Bradbury and G. Botek (2005). "Treatment for diabetic foot ulcers." *Lancet* 366(9498): 1725-1735.
- Centers for Disease Control and Prevention, A. (2005). "Data and Trends: National Diabetes Surveillance System." National Center for Chronic Disease Prevention and Health Promotion 2006.
- Chao, C. Y. L. and G. L. Y. Cheing (2009). "Microvascular dysfunction in diabetic foot disease and ulceration." *Diabetes/Metabolism Research and Reviews* 25(7): 604-614.
- D'Ambrogi, E., C. Giacomozzi, V. Macellari and L. Uccioli (2005). "Abnormal foot function in diabetic patients: the altered onset of Windlass Mechanism." *Diabet Med* 22(12): 1713-1719.

- Davis, W. A., P. E. Norman, D. G. Bruce and T. M. E. Davis (2006). "Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: the Fremantle Diabetes Study." *Diabetologia* 49(11): 2634-2641.
- DCCT (1993). "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group." *New England Journal of Medicine* 329(14): 977-986.
- Delbridge, L., P. Perry, S. Marr, N. Arnold, D. K. Yue, et al. (1988). "Limited joint mobility in the diabetic foot: relationship to neuropathic ulceration." *Diabetic Medicine* 5(4): 333-337.
- Dinh, T., S. Scovell and A. Veves "Peripheral arterial disease and diabetes: a clinical update." *International Journal of Lower Extremity Wounds* 8(2): 75-81.
- Dinh, T. and A. Veves "Microcirculation of the diabetic foot." *Current Pharmaceutical Design* 11(18): 2301-2309.
- Edmonds, M. and A. Foster (2004). "The use of antibiotics in the diabetic foot." *American Journal of Surgery* 187(5A): 25S-28S.
- Faglia, E., C. Caravaggi, G. Clerici, A. Sganzaroli, V. Curci, et al. (2010). "Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial." *Diabetes Care* 33(7): 1419-1423.
- Field, F. K. M. (1994). "Overview of wound healing in a moist environment." *American Journal of Surgery* 167: 2S-6S.
- Fleischli, J. E., R. B. Anderson and W. H. Davis (1999). "Dorsiflexion metatarsal osteotomy for treatment of recalcitrant diabetic neuropathic ulcers." *Foot & Ankle International* 20(2): 80-85.
- Fromy, B., P. Abraham, C. Bouvet, B. Bouhanick, P. Fressinaud, et al. (2002). "Early decrease of skin blood flow in response to locally applied pressure in diabetic subjects." *Diabetes* 51(4): 1214-1217.
- Frykberg, R. G., D. G. Armstrong, J. Giurini, A. Edwards, M. Kravette, et al. (2006). "Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons." *Journal of Foot & Ankle Surgery* 39(5 Suppl): S1-60.
- Frykberg, R. G., L. A. Lavery, H. Pham, C. Harvey, L. Harkless, et al. (1998). "Role of neuropathy and high foot pressures in diabetic foot ulceration." *Diabetes Care* 21(10): 1714-1719.
- Gershater, M. A., M. Londahl, P. Nyberg, J. Larsson, J. Thorne, et al. (2009). "Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study." *Diabetologia* 52(3): 398-407.
- Ghanassia, E., L. Villon, J. F. Thuan Dit Dieudonne, C. Boegner, A. Avignon, et al. (2008). "Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study." *Diabetes Care* 31(7): 1288-1292.
- Giacomozzi, C., E. D'Ambrogi, S. Cesinaro, V. Macellari and L. Uccioli "Muscle performance and ankle joint mobility in long-term patients with diabetes." *BMC Musculoskeletal Disorders* 9: 99.
- Global Lower Extremity Amputation Study, G. (2000). "Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. The Global Lower Extremity Amputation Study Group." *British Journal of Surgery* 87(3): 328-337.

- Greenman, R. L., L. Khaodhiar, C. Lima, T. Dinh, J. M. Giurini, et al. (2005). "Foot Small Muscle Atrophy Is Present Before the Detection of Clinical Neuropathy." *Diabetes Care* 28(6): 1425-1430.
- Hamdy, O., K. Abou-Elenin, F. W. LoGerfo, E. S. Horton and A. Veves (2001). "Contribution of nerve-axon reflex-related vasodilation to the total skin vasodilation in diabetic patients with and without neuropathy." *Diabetes Care* 24(2): 344-349.
- Holewski, J. J., K. M. Moss, R. M. Stess, P. M. Graf and C. Grunfeld (1989). "Prevalence of foot pathology and lower extremity complications in a diabetic outpatient clinic. [Review] [39 refs]." *Journal of Rehabilitation Research & Development* 26(3): 35-44.
- Holstein, P., M. Lohmann, M. Bitsch and B. Jorgensen (2004). "Achilles tendon lengthening, the panacea for plantar forefoot ulceration?" *Diabetes/Metabolism Research Reviews* 20 Suppl 1: S37-40.
- Hunt, T. K. and M. P. Pai (1972). "The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis." *Surgery, Gynecology & Obstetrics* 135(4): 561-567.
- Izumi, Y., K. Satterfield, S. Lee and L. B. Harkless (2006). "Risk of reamputation in diabetic patients stratified by limb and level of amputation: a 10-year observation." *Diabetes Care* 29(3): 566-570.
- Johannesson, A., G.-U. Larsson, N. Ramstrand, A. Turkiewicz, A.-B. Wirehn, et al. (2009). "Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations." *Diabetes Care* 32(2): 275-280.
- Kannel, W. B. (1985). "Framingham study insights on diabetes and cardiovascular disease." *Clinical Chemistry* 57(2): 338-339.
- Knighton, D. R., B. Halliday and T. K. Hunt (1986). "Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance." *Archives of Surgery* 121(2): 191-195.
- Koitzka, A., P. Abraham, B. Bouhanick, D. Sigaud-Roussel, C. Demiot, et al. (2004). "Impaired pressure-induced vasodilation at the foot in young adults with type 1 diabetes." *Diabetes* 53(3): 721-725.
- Krasner Diane L; Rodeheaver, G. T. S., R Gary, Ed. (2007). *Chronic Wound Care: A clinical source book for healthcare professionals*. Malvern, PA, HMP Communications.
- Krishnan, S., F. Nash, N. Baker, D. Fowler and G. Rayman (2008). "Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit." *Diabetes Care* 31(1): 99-101.
- Landsman, A. S., D. F. Meaney, R. S. Cargill, 2nd, E. J. Macarak and L. E. Thibault (1995). "1995 William J. Stickel Gold Award. High strain rate tissue deformation. A theory on the mechanical etiology of diabetic foot ulcerations." *Journal of the American Podiatric Medical Association* 85(10): 519-527.
- Larsson, J., C. D. Agardh, J. Apelqvist and A. Stenstrom (1997). "Long-term prognosis after healed amputation in patients with diabetes." *Clinical Orthopaedics & Related Research*(350): 149-158.
- Lavery, L. A., D. G. Armstrong, R. P. Wunderlich, J. Tredwell and A. J. M. Boulton (2003). "Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology

- in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort." *Diabetes Care* 26(5): 1435-1438.
- Lavery, L. A., H. R. Ashry, W. van Houtum, J. A. Pugh, L. B. Harkless, et al. (1996). "Variation in the incidence and proportion of diabetes-related amputations in minorities." *Diabetes Care* 19(1): 48-52.
- Lavery, L. A., W. H. van Houtum, H. R. Ashry, D. G. Armstrong and J. A. Pugh (1999). "Diabetes-related lower-extremity amputations disproportionately affect Blacks and Mexican Americans." *Southern Medical Journal* 92(6): 593-599.
- Levy, D. M., S. S. Karanth, D. R. Springall and J. M. Polak "Depletion of cutaneous nerves and neuropeptides in diabetes mellitus: an immunocytochemical study." *Diabetologia* 32(7): 427-433.
- Lipsky, B. A., A. R. Berendt, H. G. Deery, J. M. Embil, W. S. Joseph, et al. (2004). "Diagnosis and treatment of diabetic foot infections.[Reprint in *Plast Reconstr Surg.* 2006 Jun;117(7 Suppl):212S-238S; PMID: 16799390]." *Clinical Infectious Diseases* 39(7): 885-910.
- Londahl, M., K. Fagher and P. Katzman (2011). "What is the role of hyperbaric oxygen in the management of diabetic foot disease?" *Current Diabetes Reports* 11(4): 285-293.
- Malik, R. A., S. Tesfaye, S. D. Thompson, A. Veves, A. K. Sharma, et al. (1993). "Endoneurial localisation of microvascular damage in human diabetic neuropathy." *Diabetologia* 36(5): 454-459.
- Margolis, D. J., L. Allen-Taylor, O. Hoffstad and J. A. Berlin (2005). "Healing diabetic neuropathic foot ulcers: are we getting better?" *Diabetic Medicine* 22(2): 172-176.
- Melton, L. J., 3rd, K. M. Macken, P. J. Palumbo and L. R. Elveback (1980). "Incidence and prevalence of clinical peripheral vascular disease in a population-based cohort of diabetic patients." *Diabetes Care* 3(6): 650-654.
- Morris, A. D., R. McAlpine, D. Steinke, D. I. Boyle, A. R. Ebrahim, et al. (1998). "Diabetes and lower-limb amputations in the community. A retrospective cohort study. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit." *Diabetes Care* 21(5): 738-743.
- Moulik, P. K., R. Mtonga and G. V. Gill (2003). "Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology." *Diabetes Care* 26(2): 491-494.
- Mueller, M. J., M. Hastings, P. K. Commean, K. E. Smith, T. K. Pilgram, et al. (2003). "Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy." *Journal of Biomechanics* 36(7): 1009-1017.
- Mueller, M. J., S. D. Minor, J. E. Diamond and V. P. Blair, III (1990). "Relationship of foot deformity to ulcer location in patients with diabetes mellitus." *Physical Therapy* 70(6): 356-362.
- Mueller, M. J., D. R. Sinacore, M. K. Hastings, M. J. Strube and J. E. Johnson (2003). "Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial." *Journal of Bone & Joint Surgery - American Volume* 85-A(8): 1436-1445.
- Murray, H. J., M. J. Young, S. Hollis and A. J. Boulton (1996). "The association between callus formation, high pressures and neuropathy in diabetic foot ulceration." *Diabetic Medicine* 13(11): 979-982.
- Nabuurs-Franssen, M. H., R. Slegers, M. S. P. Huijberts, W. Wijnen, A. P. Sanders, et al. (2005). "Total contact casting of the diabetic foot in daily practice: a prospective follow-up study." *Diabetes Care* 28(2): 243-247.

- Nube, V. L., L. Molyneaux and D. K. Yue (2006). "Biomechanical risk factors associated with neuropathic ulceration of the hallux in people with diabetes mellitus." *Journal of the American Podiatric Medical Association* 96(3): 189-197.
- O'Loughlin, A., C. McIntosh, S. F. Dinneen and T. O'Brien (2010). "Review paper: basic concepts to novel therapies: a review of the diabetic foot. [Review] [118 refs]." *International Journal of Lower Extremity Wounds* 9(2): 90-102.
- Oyibo, S. O., E. B. Jude, I. Tarawneh, H. C. Nguyen, D. G. Armstrong, et al. (2001). "The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers." *Diabetic Medicine* 18(2): 133-138.
- Patel, A., S. MacMahon, J. Chalmers, B. Neal, L. Billot, et al. (2009). "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes." *New England Journal of Medicine* 358(24): 2560-2572.
- Petrov, O., M. Pfeifer, M. Flood, W. Chagares and C. Daniele (1996). "Recurrent plantar ulceration following pan metatarsal head resection." *Journal of Foot & Ankle Surgery* 35(6): 573-577; discussion 602.
- Pittet, D., B. Wyssa, C. Herter-Clavel, K. Kursteiner, J. Vaucher, et al. (1999). "Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up." *Archives of Internal Medicine* 159(8): 851-856.
- Prompers, L., M. Huijberts, J. Apelqvist, E. Jude, A. Piaggese, et al. (2007). "High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study." *Diabetologia* 50(1): 18-25.
- Rayman, G., S. T. M. Krishnan, N. R. Baker, A. M. Wareham and A. Rayman (2004). "Are we underestimating diabetes-related lower-extremity amputation rates? Results and benefits of the first prospective study." *Diabetes Care* 27(8): 1892-1896.
- Reiber, G. E., L. Vileikyte, E. J. Boyko, M. del Aguila, D. G. Smith, et al. (1999). "Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings." *Diabetes Care* 22(1): 157-162.
- Resnick, H. E., E. A. Carter, J. M. Sosenko, S. J. Henly, R. R. Fabsitz, et al. (2004). "Incidence of lower-extremity amputation in American Indians: the Strong Heart Study." *Diabetes Care* 27(8): 1885-1891.
- Resnick, H. E., P. Valsania and C. L. Phillips (1999). "Diabetes mellitus and nontraumatic lower extremity amputation in black and white Americans: the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1992." *Archives of Internal Medicine* 159(20): 2470-2475.
- Ribu, L., B. R. Hanestad, T. Moum, K. Birkeland and T. Rustoen (2007). "A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population." *Quality of Life Research* 16(2): 179-189.
- Ruef, J., M. Hofmann and J. Haase (2004). "Endovascular interventions in iliac and infrainguinal occlusive artery disease." *Journal of Interventional Cardiology* 17(6): 427-435.
- Salsich, G. B., M. J. Mueller, M. K. Hastings, D. R. Sinacore, M. J. Strube, et al. (2005). "Effect of Achilles tendon lengthening on ankle muscle performance in people with diabetes mellitus and a neuropathic plantar ulcer." *Physical Therapy* 85(1): 34-43.

- Schofield, C. J., G. Libby, G. M. Brennan, R. R. MacAlpine, A. D. Morris, et al. (2006). "Mortality and hospitalization in patients after amputation: a comparison between patients with and without diabetes." *Diabetes Care* 29(10): 2252-2256.
- Schofield, C. J., N. Yu, A. S. Jain and G. P. Leese (2009). "Decreasing amputation rates in patients with diabetes-a population-based study." *Diabetic Medicine* 26(8): 773-777.
- Singh, N., D. G. Armstrong and B. A. Lipsky (2005). "Preventing foot ulcers in patients with diabetes." *JAMA* 293(2): 217-228.
- Skoutas, D., N. Papanas, G. S. Georgiadis, V. Zervas, C. Manes, et al. (2009). "Risk factors for ipsilateral reamputation in patients with diabetic foot lesions." *International Journal of Lower Extremity Wounds* 8(2): 69-74.
- Smith, D. G., B. C. Barnes, A. K. Sands, E. J. Boyko and J. H. Ahroni (1997). "Prevalence of radiographic foot abnormalities in patients with diabetes." *Foot & Ankle International* 18(6): 342-346.
- Sohn, M.-W., R. M. Stuck, M. Pinzur, T. A. Lee and E. Budiman-Mak (2010). "Lower-extremity amputation risk after charcot arthropathy and diabetic foot ulcer." *Diabetes Care* 33(1): 98-100.
- Stansberry, K. B., H. R. Peppard, L. M. Babyak, G. Popp, P. M. McNitt, et al. (1999). "Primary nociceptive afferents mediate the blood flow dysfunction in non-glabrous (hairy) skin of type 2 diabetes: a new model for the pathogenesis of microvascular dysfunction." *Diabetes Care* 22(9): 1549-1554.
- Stansberry, K. B., S. A. Shapiro, M. A. Hill, P. M. McNitt, M. D. Meyer, et al. (1996). "Impaired peripheral vasomotion in diabetes." *Diabetes Care* 19(7): 715-721.
- Sun, P. C., H. D. Lin, S. H. Jao, R. C. Chan, M. J. Kao, et al. (2008). "Thermoregulatory sudomotor dysfunction and diabetic neuropathy develop in parallel in at-risk feet." *Diabetic Medicine* 25(4): 413-418.
- Tecilazich, F., T. Dinh and A. Veves (2011). "Treating diabetic ulcers. [Review]." *Expert Opinion on Pharmacotherapy* 12(4): 593-606.
- Tentolouris, N., S. Al-Sabbagh, M. G. Walker, A. J. M. Boulton and E. B. Jude (2004). "Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study." *Diabetes Care* 27(7): 1598-1604.
- Tentolouris, N., K. Marinou, P. Kokotis, A. Karanti, E. Diakoumopoulou, et al. (2009). "Sudomotor dysfunction is associated with foot ulceration in diabetes." *Diabetic Medicine* 26(3): 302-305.
- Tesfaye, S., A. J. M. Boulton, P. J. Dyck, R. Freeman, M. Horowitz, et al. (2010). "Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments." *Diabetes Care* 33(10): 2285-2293.
- UKPDS (1998). "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.[Erratum appears in *Lancet* 1999 Aug 14;354(9178):602]." *Lancet* 352(9131): 837-853.
- Vamos, E. P., A. Bottle, M. E. Edmonds, J. Valabhji, A. Majeed, et al. (2010). "Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008." *Diabetes Care* 33(12): 2592-2597.
- van Schie, C. H. B., A.J. M. Boulton (2006). *Biomechanics of the Diabetic Foot: The Road to Foot Ulceration*. The Diabetic Foot. A. G. Veves, J.M.; LoGerfo, F.W. Totowa, NJ, Humana Press Inc.: 185-200.

- Veves, A., C. M. Akbari, J. Primavera, V. M. Donaghue, D. Zacharoulis, et al. (1998). "Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration." *Diabetes* 47(3): 457-463.
- Veves, A. and G. L. King (2001). "Can VEGF reverse diabetic neuropathy in human subjects?" *Journal of Clinical Investigation* 107(10): 1215-1218.
- Veves, A., H. J. Murray, M. J. Young and A. J. Boulton (1992). "The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study." *Diabetologia* 35(7): 660-663.
- Vinik, A. I., R. E. Maser, B. D. Mitchell and R. Freeman (2003). "Diabetic autonomic neuropathy. [Review] [192 refs]." *Diabetes Care* 26(5): 1553-1579.
- Wild, S., G. Roglic, A. Green, R. Sicree and H. King (2004). "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030." *Diabetes Care* 27(5): 1047-1053.
- Young, M. J., P. R. Cavanagh, G. Thomas, M. M. Johnson, H. Murray, et al. (1992). "The effect of callus removal on dynamic plantar foot pressures in diabetic patients." *Diabetic Medicine* 9(1): 55-57.
- Zimny, S., H. Schatz and M. Pfohl (2004). "The Role of Limited Joint Mobility in Diabetic Patients With an At-Risk Foot." *Diabetes Care* 27(4): 942-946.
- Zoungas, S., B. E. de Galan, T. Ninomiya, D. Grobbee, P. Hamet, et al. (2008). "Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial." *Diabetes Care* 32(11): 2068-2074.

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.