Diabetic foot: Disease, complication or syndrome?

Afseeh Alavi, Mariam Botros, Janet L Kuhnke, David Armstrong, Giuseppe Papia, Julia Lowe, Kevin Woo, R Gary Sibbald

Diabetes is the sixth leading cause of death in North America. The number of Canadian with diabetes is projected to rise to 4.2 million people by 2020. Diabetic foot ulcers have been reported in 25% of individuals with diabetes and those with foot ulcers have an increased risk of amputation and increased mortality. The earlier recognition of the high-risk foot and the timely treatment will save legs and lives. An inter-professional approach is pivotal to support patients’ needs.

Diabetic foot complications are a challenge that is growing worldwide. The care of patients with such problems requires an interprofessional approach within a complex communication network for collaborative and integrative care. Foot complications as a result of diabetes cover a heterogeneous group of disorders including neuropathy, foot deformity, ischemia, chronic ulceration and Charcot foot.

Most diabetic foot abnormalities take an indolent course, but the disease can lead to significant disfigurement, adversely impacting daily life and exposing patients to life threatening events, such as infection (Jeffcoate et al, 2008) and ischemia (Lipsky, 1997). The mortality rates associated with complications following diabetic foot disease are widely accepted to be equivalent to those of aggressive forms of cancer (Armstrong, 2007; Lavery et al, 2010; Armstrong and Mills, 2013). In fact, the 5-year mortality rate for individuals with a neuropathic ulcer is higher than that of patients with Hodgkin’s disease, breast cancer or prostate cancer. The 5-year mortality in individuals with neuroischemic ulcers is even higher than in colon cancer (Armstrong, 2007; Edmonds, 2010).

More than 20 Canadians are diagnosed with diabetes every hour (CDA, 2009). The known cases of diabetes in Canada represent 2.7 million people (7.6%) in 2010, which is projected to rise to 4.2 million people (10.8%) by 2020, but it is estimated that an additional 700,000 persons have the disease but are unaware and undiagnosed (CDA, 2009). In Canada, by 2019 that number is expected to grow to 3.7 million. (CDA, 2008). The Canadian economic cost of treating diabetic foot disease is spiralling out of control. The Chronic Disease Care Model (Improving Chronic Illness Care, 2012) supports systems, teams, and individuals in delivering effective, evidence-based, outcome-focused services (Figure 1).

While a diabetic foot ulcer is a personal crisis, and a pivotal event in the life history of that patient, it is also a financial challenge for the healthcare system. The economic burden of diabetes in Canada was expected to be about $12.2 billion in 2010, and the direct cost of diabetes now accounts for about 3.5% of public healthcare spending and this figure continues to rise (CDA, 2009). More than 333 million people worldwide will develop diabetes by 2025, creating a growing healthcare issue with a huge cost burden (Narayan et al, 2003; Wild et al, 2004). People with diabetes have a 25% lifetime risk of developing a foot ulcer with an annual incidence of 2% (Abbott et al, 1998). Diabetic foot ulcers are the most common reason for diabetes-related hospitalisation.

The risk of lower extremity amputation in a person with diabetes is 23-times higher than in people without diabetes (Lavery and Armstrong, 2007). While amputation is the most preventable complication of diabetic foot disease, it is preceded by foot ulceration in more than 85% of major amputations (Pecoraro et al, 1990).

Foot complications are also indicators of poor diabetic sugar control (elevated A1c) and other management issues, including elevated blood
Foot complications are also indicators of poor diabetic sugar control (elevated A1c) and other management issues, including elevated blood pressure, cholesterol, obesity, mental health, and mood disorders (depression).

There is a need to acknowledge that diabetic foot abnormalities are a disease entity or syndrome similar to retinopathy and nephropathy. We need to raise awareness in healthcare providers and policy makers concerning the person with diabetes and their increased risk of foot ulcers, poor healing, and foot amputation.

A medical complication is an unfavorable evolution of foot disease leading to a worsening of signs, symptoms and/or new pathological changes. The diabetic foot disease repair process is the product of a well-orchestrated integration of complex events of cell migration, cytokine production, angiogenesis and extracellular matrix deposition. These fundamental processes are similar to tissue regeneration after successful treatment of neoplasia. This raises the question whether changes associated with the diabetic foot represent a new disease phenomenon developing in people with diabetes or whether they are a simple complication of diabetes.

Etiology of diabetic foot complications
Diabetic foot changes are the result of several contributory factors, such as peripheral neuropathy, vascular changes and foot deformities. Assessment and treatment of the contributing factors is essential for optimal prevention and management (Boulton et al, 2008; Bakker et al, 2011). This requires a comprehensive foot examination, risk assessment and clear communication with the individual as to the status of their foot (Table 1).

Neuropathy and deformity
Damage to the nerve fibers is the result of hyperglycemia, dyslipidemia, insulin resistance, and oxidative stress, which can lead to cellular and endothelial damage through different pathways (Edmonds, 1986; 2010). Peripheral neuropathy leads to both somatic and autonomic damage. The damage to small fibers leads to a predominant loss of pain and thermal sensation before blunting light touch and vibration sensation (Edmonds, 1986; 2010).

The degeneration of postganglionic unmyelinated axons further leads to dry skin or hypohydrosis. Dry skin, thickness, and callus easily crack and this leads to skin fissures.

Motor fibers are affected with slowed motor conduction velocities and the reduced action potential of the intrinsic muscles of the feet. This
Multiple studies have demonstrated that more than 80% of patients with diabetic foot ulcers have neuropathy.

Table 1. Components of the foot exam (adapted from Boulton et al [2008]).

<table>
<thead>
<tr>
<th>Essential features of history</th>
<th>Key components of the diabetic foot exam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Past history</strong></td>
<td><strong>Inspection</strong></td>
</tr>
<tr>
<td>• Ulceration</td>
<td>• Dermatologic</td>
</tr>
<tr>
<td>• Amputation</td>
<td>• Skin status: colour, thickness, dryness, cracking</td>
</tr>
<tr>
<td>• Charcot joint</td>
<td>• Sweating</td>
</tr>
<tr>
<td>• Vascular surgery</td>
<td>• Infection: check between the toes for fungal infection</td>
</tr>
<tr>
<td>• Angioplasty</td>
<td>• Ulceration</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
<td>• Calluses / blistering: hemorrhage into callus</td>
</tr>
<tr>
<td><strong>Neuropathic symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>• Positive (e.g. burning or shooting pain, electrical or sharp sensations, etc.)</td>
<td></td>
</tr>
<tr>
<td>• Negative (e.g. numbness, feet feel dead)</td>
<td></td>
</tr>
</tbody>
</table>

| **Vascular symptoms**        | **Musculoskeletal**                      |
| • Claudication               | • Deformity (e.g. claw toes, prominent metatarsals heads, Charcot joint) |
| • Rest pain                  | • Muscle wasting (gutting between metatarsals) |
| • Non-healing ulcer          |                                         |

| **Other diabetes complication** | **Neurological assessment** |
| • Renal (dialysis, transplant) | • 10-g monofilament and one of the following four: |
| • Retinal (visual impairment) | 1. Vibration using 128–Hz tuning fork |
|                               | 2. Pinprick sensation |
|                               | 3. Ankle reflexes |
|                               | 4. VPT (vibration perception threshold) testing |

| **Vascular assessment**       | **Foot pulses; ABI (ankle–brachial index) if indicated** |
|                               | |

leads to the wasting and weakness of intrinsic foot muscles and subsequent deformity (claw/hammer toes). Foot deformities can cause an abnormal distribution of plantar pressure, repeated trauma, especially with poor fitting footwear, and subsequent foot ulceration. This foot ulcer formation is often the first step to subsequent infection, local tissue necrosis and lower extremity amputation.

Multiple studies have demonstrated that more than 80% of patients with diabetic foot ulcers have neuropathy. Neuropathy, not peripheral arterial disease is considered to be the major factor predisposing persons with diabetes to osteomyelitis (Lipsky et al, 1990).

Non-enzymatic glycosylation of peri-articular soft tissues may limit joint motion in the person with diabetes, and neuropathy that can lead to atrophy of the intrinsic musculature and subsequently contracture of digits (Grant et al, 1990). This decrease in the foot’s ability to accommodate for ambulatory ground reactive forces increases plantar pressures (Frykberg et al, 1998; Armstrong et al, 1999). Additionally, glycosylation may deleteriously affect the resilience of the Achilles tendon, causing shortening or loss of natural extensibility, resulting in the foot being pulled into plantar flexion. The subsequent increased forefoot pressure and even mid-foot collapse can set the stage for a potential Charcot arthropathy. Examination of the feet for structural abnormalities and reduced joint mobility is critical in helping identify pressure points that are susceptible to future ulceration.

**Ischemia**

The underlying autonomic denervation may be responsible for vascular abnormalities, with the resting blood flow in a neuropathic foot five times higher than in a normal foot. The increased arterial flow to the limb leads to higher blood supply to the bones and potential osteolytic abnormalities. Medial wall calcification can cause arterial stiffness and increased pulse wave velocity in a neuropathic limb.

Peripheral arterial disease (PAD) is present in more than 50% of patients with diabetic foot ulceration. Peripheral arterial disease is an independent risk factor for further ulceration, and neuroischemic diabetic foot ulcers are less likely to heal and more likely to require amputation. It is crucial to screen people with diabetes for PAD.
including conducting a thorough history and physical examination in addition to noninvasive vascular studies (Edmonds, 1986).

Coexisting polyneuropathy and PAD frequently mask the symptoms of PAD and decrease the sensitivity of vascular studies (Brownrigg et al, 2013). In people with diabetes, capillary hypoperfusion leads to a further delay in wound healing. This delay in collateral formation and consequent arterial occlusion may lead to severe perfusion defects (Nabuurs-Franssen et al, 2002). Several studies have demonstrated that diabetes is a risk factor for the development of cardiovascular disease, with risk of mortality twice as high in people with diabetes; a foot ulcer further increases this risk (Brownrigg, 2012).

Ulcers
People with diabetes are at risk of developing foot ulcers due to the loss of protective sensation and structural deformities secondary to neuropathy (Figure 2). The diabetic foot is biologically compromised and the major underlying cause is deformity from peripheral neuropathy and ischemia from peripheral arterial disease. Once skin integrity is compromised, foot ulcers may lead to other complications, partly due to a compromised immune system.

Immune function abnormalities
Wound healing and neutrophil function are impaired by hyperglycemia, necessitating good glycemic control. In a study by Van den Bergh et al, intensive intravenous insulin therapy was administered to maintain blood glucose at or below 6.2mmol/L. The intravenous insulin reduced morbidity and mortality among critically ill surgical intensive care patients (Van den Bergh, 2001). However, subsequent studies have failed to confirm this observation. A meta-analysis, including NICE-SUGAR study data (Griesdale, 2009) of intensive insulin therapy and mortality among critically ill patients, documented increased mortality related to hypoglycemia. Most guidelines now recommend adopting a more conservative approach with blood glucose levels maintained between 7.8-11.1 mmol/L (Umpierrez, 2012; CDA, 2013).

Deep and surrounding tissue infection can be a major threat to limb and life and should be treated promptly. Diabetic foot infection (DFI) is defined clinically as a soft tissue or joint/bone infection anywhere distal to the malleolus. It commonly affects the toes followed by mid foot. Infection usually starts with colonisation of neuropathic or ischemic ulcers, or alternately may develop from small fissures between the toes or nail beds. The underlying ulcer base and surrounding tissues are susceptible to bacterial colonisation and, with decreased host resistance, critical colonisation and possible subsequent deep and surrounding infection.

The progression from wound colonisation to infection is influenced by various factors including:
- Type and depth of the wound.
- Blood supply.
- Immune status of the patient.
- Quantity and virulence of colonising organisms.

DFI remains a challenge to manage because of coexisting neuropathy, potential vascular changes, diabetes-related immune deficiencies and foot deformities.

Data from 14 hospitals in 10 European countries demonstrated that 58% of diabetic foot ulcers in 1229 successive patients were infected, with 82% infection rates in those admitted to hospital. Almost half of the patients (45%) had deep ulcers that extended into tissue below the subcutis, for example, tendons, muscle or bone (Prompers et al, 2007).

Conclusion
Diabetes is the most common cause of non-traumatic lower limb amputations (Armstrong and Lavery, 1998; Rogers and Bevilacqua, 2010). Foot ulcers and amputations reduce quality of life, increase mortality and involve lengthy hospital admissions (Rogers and Bevilacqua, 2010). The diabetic foot is certainly a complex multifactorial process that is more than an associated disease complication. In order to diminish the detrimental consequences associated with diabetic foot complications we need an overall structure that is designed to meet the needs of patients requiring preventative and often chronic maintenance care, rather than simply responding to acute problems when they occur. We must move from a reactive healthcare system to one that keeps its people with diabetes-related foot
disease as healthy as possible, addressing their foot care needs through planning, proven healthcare delivery strategies and management. However, once problems develop, these patients require aggressive management involving a coordinated interprofessional team with medical, wound and vascular care, ideally in a single center.

In many European centers, integrated coordinated care has greatly improved quality of life and patient outcomes for people with diabetes. We need an increased Canadian emphasis on the prevention and management of diabetic foot disease.

Authors
Ahmeh Alavi, Department of Medicine (Dermatology), University of Toronto and Wound Care Center, Women College Hospital, Toronto. Mariam Botros, Wound Care Center, Women College Hospital, Toronto. Janet L. Kuhnke, PhD Student, St Lawrence / Laurentian University BSN Collaborative Program, Cornwall. David Armstrong, Department of Surgery, University of Arizona.


“We must move from a reactive healthcare system to one that keeps its people with diabetes-related foot disease as healthy as possible.”