

# The foot in diabetes – a reminder of an ever-present risk

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## ABSTRACT

The term ‘diabetic foot disease’ (DFD) often signifies the presence of foot ulceration and infection, but one must also be wary of the rarer occurrence of Charcot foot disease. The worldwide prevalence of DFD is 6.3% (95%CI: 5.4–7.3%). Foot complications present a major challenge to both patients and healthcare systems, with increased rates of hospitalisation and an almost trebled 5-year mortality. The Charcot foot often occurs in patients with long-standing diabetes, presenting as an inflamed or swollen foot or ankle, following unrecognised minor trauma. This review focuses on the prevention and early identification of the ‘at-risk’ foot. DFD is best managed by a multi-disciplinary foot clinic team consisting of podiatrists and healthcare professionals. This ensures a combination of expertise and provision of a multi-faceted evidence-based treatment plan. Current research using endothelial progenitor cells (EPC) and mesenchymal stem cells (MSC) offers a new dimension in wound management.

**KEYWORDS:** Diabetic foot disease, infections, prevention

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## Introduction

The global burden of diabetes mellitus and diabetic foot disease (DFD) is exponentially increasing with life expectancy.<sup>1,2</sup> Diabetic foot problems are most commonly seen in patients with long-standing and inadequately controlled diabetes.<sup>3</sup> These complications negatively impact on patients’ quality of life as well as on their socio-economic wellbeing.<sup>4</sup> Patients with foot ulcers have an almost three-fold increased risk of death at 5 years compared to those without foot complications.<sup>5</sup> Studies also show that dialysis-dependent patients with amputations have a 5-year mortality risk of more than 70%.<sup>6</sup>

## Epidemiology and pathophysiology

A meta-analysis by Zhang *et al*<sup>1</sup> showed that the global prevalence of diabetic foot complications is 6.3% (95%CI: 5.4–7.3%). Males have a higher prevalence rate of DFD than

females<sup>7–9</sup> (4.5%, 95%CI: 3.7–5.2% vs 3.5%, 95%CI: 2.8–4.2%). The prevalence of DFD at GP practices in the UK in 2008 was estimated at 7.6% (95% CI: 6.6–8.6) for people with type 1 diabetes and 8.5% (95% CI: 8.2–8.8) for those with type 2 diabetes.<sup>10</sup>

Foot complications are commoner in patients of African or Native-American descent and these patients tend to have longer hospital stays with adverse outcomes.<sup>11</sup> Diminished bioavailability of nitric oxide and impaired endothelium-dependent vasodilatation are postulated mechanisms for worse outcomes in these patients when compared to White patients.<sup>12</sup>

Various factors, including impaired sensation related to neuropathy, abnormal gait and the presence of ischaemia due to peripheral artery disease (PAD), contribute to the development of DFD.<sup>13,14</sup> Sensory neuropathy predisposes to repeated microtrauma, callus formation and subcutaneous haemorrhage, leading to skin ulceration.<sup>15,16</sup> The exact prevalence of Charcot arthropathy remains unknown, partly because of a lack of standardised diagnostic criteria. One study looked at point prevalence in the East Midlands’ secondary care services over a 1-month period. Ninety cases were found, representing 4.3 per 10,000 of the 205,033 persons with diabetes.<sup>17</sup>

Diabetic foot ulceration (DFU) increases the rates of hospital admissions and is still the commonest cause of non-traumatic lower extremity amputation in the developed world.<sup>18</sup> Foot ulceration is a major cause of psychosocial distress.<sup>19</sup> The European Study Group on Diabetes and the Lower Extremity (Eurodiale) study recruited patients with a new foot ulcer. This was a prospective observational study. 18% of these subjects underwent a minor amputation while 5% of subjects required a major amputation within 1 year of follow up.<sup>20</sup> Male patients are also more likely to undergo amputations at a younger age.<sup>21–23</sup> Such differences may be secondary to variations in personal hygiene, self-examination and walking patterns (eg walking barefoot).<sup>24,25</sup>

Diabetic neuropathy occurs in 30–50% of patients with long-standing diabetes.<sup>26–29</sup> The imbalance between mitochondrial and cytosolic reactive oxygen species in patients with vascular problems can lead to axonal nerve damage with progressive distal-to-proximal sensory loss.<sup>30,31</sup> In unmyelinated small C fibres, this imbalance can result in painful diabetic neuropathy<sup>32,33</sup> and this can sometimes be difficult to distinguish from ischaemic pain. In the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study, diabetic neuropathy was already present in 6% of patients with type 1 diabetes at the time of diagnosis, increasing to 30% after 13 years of follow up.<sup>34,35</sup> The Action to

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Control Cardiovascular Risk in Diabetes (ACCORD) Trial and the Veteran Affairs Diabetes Trial (VADT) showed that neuropathy affects 42% of patients with type 2 diabetes at diagnosis.<sup>36,37</sup> Hypertension, dyslipidaemia, and impaired glucose regulation have all been implicated in both the aetiology and progression of diabetic neuropathy.<sup>38,39</sup>

Sensory neuropathy and abnormal vascularity, as well as external factors such as callus formation and abnormal foot pressures, hamper wound healing. Wound healing involves a synchronous process of coagulation, inflammation, cell migration and proliferation, with extracellular matrix (ECM) deposition.<sup>40</sup> This is normally followed by re-epithelisation and a return of tissue function. Growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)  $\beta$ 1 and tissue plasminogen activator (TPA) are all involved in wound healing and ECM deposition. In patients with diabetes, wounds may abnormally stall in some phases of healing<sup>41,42</sup> due to the body's inability to recruit cells and re-build tissue within the damaged area.<sup>43</sup> Defective angiogenesis also plays a role in the aetiology of the microvascular and macrovascular complications of diabetes. Excessive reactive oxygen species result in instability of the extracellular matrix and altered Vascular Endothelial Growth Factor (VEGF) sensitivity, leading to inadequate vascularity and abnormal healing.<sup>41,44,45</sup>

### Risk assessment, prevention and management

Regular foot inspection enables early recognition of skin damage such as callus formation, blistering or haemorrhage, all of which are strong predictors of ulceration.<sup>46–49</sup> Patients with callus formation have an 11-fold increased risk of diabetic foot ulceration compared to those without.<sup>50</sup> Both patients and healthcare professionals should be educated on recognising early warning signs of foot ulceration (pedal skin dryness, hyperkeratosis and callus formation) with prompt specialist podiatric referral where necessary. At-risk patients can be prescribed urea-based emollients that help reduce epidermal thickness and also have antimicrobial properties.<sup>51,52</sup>

Frequency of foot screening depends on loss of protective sensation (LOPS) and ulceration risk in accordance with the

International Working Group on the Diabetic Foot (IWGDF) 2019 Risk Stratification System<sup>3</sup> (Table 1), but in the general diabetes population, annual screening usually suffices. Once diabetic neuropathy has developed, further screening visits are not necessary, and the patient should be reviewed regularly in a foot protection programme.

Tactile sensation assessed by means of a 10 g Semmes Weinstein monofilament, and vibration sensation using a neurothesiometer, are both useful in assessing risk of foot ulceration.<sup>53–55</sup> The neurothesiometer has a handheld probe, which is applied to the great toe and the stimulus is gradually increased until the patient can feel the vibratory sensation.<sup>56,57</sup> This measurement is recorded in Volts as a vibration perception threshold (VPT). Vascular status can be carried out at the bedside by clinical palpation of pedal pulses, or more formally using an ultrasound doppler. The VibraScan is a recently developed software-based tool which uses artificial intelligence to measure VPT and can provide information about the extent of diabetic neuropathy with reliable accuracy.<sup>57</sup>

PAD is an independent risk factor for non-healing ulceration, infection and amputation.<sup>58</sup> Patients should also be asked about claudication pain, previous foot ulcers and amputations. The IWGDF recommends that revascularisation is indicated for toe pressures <30 mmHg, for a transcutaneous oxygen pressure (TcPO<sub>2</sub>) <25 mmHg, or if there is significant tissue loss or infection.<sup>3</sup> Revascularisation within 8 weeks using percutaneous transluminal angioplasty (PTA) or bypass surgery restores blood flow to the foot arteries, perfusing the wound area, and reducing amputation risk. Similar outcomes for amputation-free survival (AFS) and overall survival (OS) were observed in patients who undergo angioplasty or bypass for infra-inguinal vascular disease. However, patients who survive for at least 2 years after bypass surgery seem to have better OS and slightly better AFS.<sup>59,60</sup> Anti-platelet and lipid-lowering agents also help reduce the progression of established PAD.<sup>61</sup> The Diabetes Study of Northern California (DISTANCE), a 10-year follow up study established hypertriglyceridemia as an independent marker for lower-extremity amputations.<sup>62</sup>

Prompt diagnosis of Charcot foot is crucial to successful management. Studies have shown that a delayed diagnosis can lead to additional damage, ulceration and an increased risk of fracture.<sup>62–64</sup> The Charcot foot is classically characterised by four stages: inflammation, fragmentation, coalescence and consolidation. In the acute stage, it may be easily mistaken for cellulitis as it often presents as a warm, red, swollen foot which may also be painful. Usually, there are no changes on plain radiograph,<sup>65</sup> and magnetic resonance (MR) scanning is often required to help make a diagnosis. Early offloading and immobilisation is the mainstay of treatment in the acute stage.<sup>66</sup> This can be achieved by wearing of devices such as total contact casts and DARCO boots.<sup>3,5,67–71</sup>

Surgical interventions such as osteotomy, flexor tenotomy and Achilles tendon lengthening may be considered in patients who develop foot deformities such as hammer toes and prominent metatarsal heads.<sup>72–75</sup>

There is a general consensus that patients with diabetes and peripheral artery disease should receive anti-platelet therapy.<sup>76</sup> In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study, which enrolled 27,395 patients with stable coronary and/or peripheral artery disease, low dose

**Table 1. IWGDF 2019 Risk Stratification System<sup>3</sup>**

Category	Risk of ulceration	Characteristics	Frequency of screening
0	Very low	No LOPS or PAD	Annual
1	Low	LOPS or PAD	6–12 months
2	Moderate	LOPS + PAD LOPS + foot deformity PAD + foot deformity	3–6 months
3	High	LOPS or PAD + one or more of: > History of foot ulcer > History of amputation > End-stage kidney disease	1–3 months

Lops = loss of protective sensation; PAD = peripheral artery disease.

anti-thrombotic therapy (rivaroxaban 2.5 mg twice a day in combination with aspirin 100 mg daily) more than halved the risk of major foot complications (including amputations) and reduced both major adverse cardiovascular events (MACE) and overall mortality.<sup>77</sup>

Although hyperglycaemia impairs wound healing, the role of intensive glucose control is still being studied.<sup>78</sup> In one study by Xiang *et al*, rates of wound healing were better in patients with a glycated haemoglobin (HbA1c) of 53–63 mmol/mol.<sup>79</sup> Euglycaemia is however imperative in the prevention of neuropathy and its consequences in both type 1 (DCCT) and type 2 diabetes (UK Prospective Diabetes Study, UKPDS).<sup>80,81</sup>

Obesity (defined as a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>) is the second most common metabolic risk factor for diabetic foot ulceration, as it increases cardiac workload and impairs tissue perfusion and healing. Interventions targeting obesity are important<sup>82</sup> and preliminary studies have shown promising effects of weight loss on improving neuropathy.<sup>83–85</sup> Glucagon-like peptide-1 receptor agonists (GLP1-RAs) have become instrumental in reducing both HbA1c and weight in routine clinical practice.<sup>86</sup> They also have proven cardioprotective effects.<sup>87,88</sup> The impact of GLP1-RAs on PAD is unknown and the ongoing STRIDE (Effects of Semaglutide on Functional Capacity in Patients with Type 2 Diabetes and peripheral artery disease) trial is aimed at investigating a possible effect of semaglutide on walking ability in persons with diabetes and symptomatic PAD.<sup>89</sup>

Lifestyle interventions including feasible exercise in addition to patient education may play a role in the management of persons with DFD,<sup>90–92</sup> but it remains unknown what the exact effect is and which educational approach is most effective.<sup>47</sup> It should however account for gender and cultural differences and must be adapted to the patient's level of ability, education and acceptance.<sup>93</sup>

Dietary factors, mainly protein intake, are important for tissue repair and wound healing. Inadequate protein intake can lead to defective angiogenesis and a poor inflammatory response, resulting in defective wound healing.<sup>94,95</sup> A balanced diet that can help address BMI while providing all the necessary nutritional requirements for wound healing is crucial in patients with diabetic foot problems. Patients with a BMI  $>40$  kg/m<sup>2</sup> should be considered for bariatric surgery (including Roux-en-Y Gastric Bypass or sleeve gastrectomy). Randomised trials by Schauer<sup>96</sup> *et al* confirmed a superiority of bariatric surgery over medical treatment on HbA1c, BMI, plasma triglycerides and quality of life (QoL). Other studies have shown partial or complete remission of diabetes following bariatric surgery.<sup>97,98</sup> Other adverse factors on wound healing include hypertension, dyslipidaemia, smoking and excessive alcohol intake<sup>99,100</sup> and should all be addressed in patients attending the foot clinic.

Diabetic foot ulcers commonly harbour contaminant or colonising pathogens, but these commensals do not usually cause active infection. Purulent secretions, a foul odour and wound undermining are important hallmarks of active infection. New ulcers need to be attended to immediately by the specialist diabetic foot team. Infection inhibits adequate wound healing by releasing bacterial enzymes with subsequent degradation of growth factors and metalloproteinase fibrins.<sup>101,102</sup> Deep tissue cultures are preferred to superficial wound swabs as the latter often identify microbial contaminants that may not warrant treatment.<sup>71</sup> Tissue probing and radiological

investigations (plain radiography, magnetic resonance imaging) are all useful for identifying foreign bodies and diagnosing osteomyelitis (NICE, 2019). Oral broad-spectrum antibiotics are initially prescribed and changed to more specific agents later on, depending on clinical response and wound culture sensitivities. Intravenous antibiotics are often used for more severe infections, particularly those with deep soft tissue and bone involvement. Wounds should be debrided and cleaned of any necrotic material and foreign bodies.<sup>20</sup> Debridement is carried out by specialist podiatrists, but deep tissue involvement may require surgical or orthopaedic intervention. Application of appropriate dressings provides an optimum environment for wound healing.<sup>103</sup> Dressings are usually selected based on TIMES assessment – Tissue, Infection, Moisture balance, Epithelialisation and surrounding Skin<sup>104,105</sup> – and on the healing stage of the wound. These should be regularly inspected and changed, particularly in exudative wounds, in order to reduce maceration of surrounding skin.<sup>106</sup>

Cell-based therapies, including endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSC), have shown encouraging results, improving pain-free walking distance, ankle-brachial pressure index (ABPI) and tissue oxygenation.<sup>107–111</sup> Recombinant growth factors, platelet-rich plasma (PRP) and leukocyte- and platelet-rich fibrin (L-PRF) are also promising new treatment methods that enhance wound healing.<sup>111</sup>

Another preliminary study recommends the use of stromal vascular fraction (SVF) for chronic diabetic ulcers.<sup>112</sup> Although MSC seem to be generally safe, there have been some reports of adverse thrombo-embolic events.<sup>113,114</sup> Larger studies will certainly help address their efficacy, safety and optimal administration route.

## Conclusion

Successful management of the diabetic foot requires a multidisciplinary team (MDT) approach consisting of specialist podiatrists, orthotists, diabetologists, diabetes nurse specialists and dietitians, as well as vascular and orthopaedic surgeons.

Prevention of foot complications remains key to limb protection and salvage, particularly in vulnerable patients and those with limited access to healthcare. As we care for patients with diabetes, we should certainly remember the still very ubiquitous presence of foot complications in hospitals, care homes and indeed the community. Despite a gargantuan milestone in diabetes care in the last decade, foot ulceration remains a persistent problem for many patients. Continuous education, not only of patients with diabetes but also of healthcare workers within all disciplines remains pivotal in the prevention and early management of this omnipresent and troublesome complication.

## Key practice implications

- Diabetic foot disease remains a common complication in patients with diabetes, with up to a prevalence of 7.6% in the UK.
- Foot complications still present a major challenge to persons with diabetes and healthcare systems, and are best managed within a multidisciplinary team setting.
- Education of patients and healthcare professionals across all medical specialties helps to identify and manage diabetic foot complications in a timely manner.

- Good glycaemic control, management of obesity and lifestyle modifications complement specialist podiatric input in wound prevention and management.
- Novel therapies with progenitor stem cells open a new horizon in wound management. ■

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