Preventing and treating foot complications associated with diabetes mellitus

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Abstract | Diabetes mellitus is associated with a series of macrovascular and microvascular changes that can manifest as a wide range of complications. Foot ulcerations affect ~2–4% of patients with diabetes mellitus. Risk factors for foot lesions include peripheral and autonomic neuropathy, vascular disease and previous foot ulceration, as well as other microvascular complications, such as retinopathy and end-stage renal disease. Ulceration is the result of a combination of components that together lead to tissue breakdown. The most frequently occurring causal pathways to the development of foot ulcers include peripheral neuropathy and vascular disease, foot deformity or trauma. Peripheral vascular disease is often not diagnosed in patients with diabetes mellitus until tissue loss is evident, usually in the form of a nonhealing ulcer. Identification of patients with diabetes mellitus who are at high risk of ulceration is important and can be achieved via annual foot screening with subsequent multidisciplinary foot-care interventions. Understanding the factors that place patients with diabetes mellitus at high risk of ulceration, together with an appreciation of the links between different aspects of the disease process, is essential to the prevention and management of diabetic foot complications.

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Introduction

Although preventable, foot problems are a common occurrence in patients with diabetes mellitus. An estimated 2–3% of patients with diabetes mellitus are thought to have an active foot ulcer and the lifetime risk of developing a foot ulcer for these patients could be as high as 25%.[1,2] Consequently, the financial and health burdens of diabetic foot disease is substantial and in 2010–2011 was estimated to cost the National Health Service in the UK at least UK£580 million, which represents ~0.6% of the national health expenditure in that period of time.[3] More than half of this cost was estimated to be spent on care of ulcerations in the community, but the cost of inpatient care for foot ulcers and other foot complications in patients with diabetes mellitus is estimated at >£219 million in the UK.[3] Unfortunately, despite the enormous financial burden of managing diabetic foot disease, funding for research in this area is disappointingly low.[4]

In addition to being prevalent and costly, diabetic foot problems are associated with considerable morbidity and mortality. In fact, patients with diabetes-related wounds and amputations have been suggested to have worse outcomes than patients with some forms of cancer.[5] Indeed, the risk of mortality observed in patients with diabetes mellitus receiving dialysis treatment and who have already undergone an amputation is worse than the mortality associated with almost every cancer.[6] This increased risk of mortality is partly a consequence of the multi-systemic nature of diabetes mellitus; patients with diabetes mellitus and foot problems frequently have other major microvascular complications, as well as macrovascular disease, which contributes to the increased risk.[7] Peripheral vascular disease (PVD) is defined as disease of the arteries outside the heart and brain, which mostly results in an impairment of blood supply to the legs and is found in ~20% of all people aged over 60 years.[8] Although many diabetic foot problems are preventable, patients frequently present late in the natural history of the condition, often because they have lost the 'gift of pain' as a consequence of neuropathy, which normally protects the lower extremities from repetitive minor trauma.[9]

In this Review, we discuss the major factors that contribute to foot problems in patients with diabetes mellitus, namely PVD, peripheral neuropathy and other microvascular complications, as well as the common pathways that result in ulceration. The importance of prevention, assessment and management of diabetic foot ulcers, infection and the need for a multidisciplinary approach are also addressed.

Epidemiology

The risk of foot lesions increases with both age and duration of diabetes mellitus.[2,10,11] Additionally, male patients have a 1.6-fold increased risk of developing ulcers compared with female patients.[2,10] With respect to ethnicity, patients of European origin seem to have higher risks of foot ulcers and amputations than patients of Indian subcontinent, Asian or African-Caribbean ancestry.[12] Patients with diabetes mellitus who have already had a previous ulcer or amputation are among those with highest risk of

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Key points

- A comprehensive foot examination is essential for the appropriate assessment, prevention and management of diabetic foot complications
- Peripheral neuropathy is concurrent with 90% of foot ulcers and is a major contributor to the development of ulcers in patients with diabetes mellitus
- Many patients with diabetes mellitus who have peripheral vascular disease are asymptomatic until they develop tissue loss
- In the context of tissue loss, increasing ischaemia elevates the risk of limb loss and, therefore, healing usually requires revascularization
- Revascularization can be performed using endovascular or open surgery techniques, or a combination of both, and depends on the patient's health, the location of the disease and local surgical expertise
- Offloading, debridement, antibiotics, optimal glycaemic control and a multidisciplinary team are fundamental to the effective treatment of diabetic foot complications

future foot problems.[13] The investigators in a number of studies have attempted to assess both the incidence and prevalence of foot ulceration and amputation over the past 20 years.[10,14] However, direct comparisons between these studies are difficult as the reported frequencies of foot ulceration vary considerably, which might be the result of different diagnostic criteria and/or regional differences.[15] The prevalence of active ulceration in patients with diabetes mellitus varies between 1% and 5%, with the prevalence of amputation being slightly more than 1%.[16] Among studies in different European countries, the reported annual incidence of foot ulcers is ~2%.[10,11,16] Importantly, the proportion of patients with diabetes mellitus who are at increased risk of foot ulceration, such as elderly patients (>65 years of age) with type 2 diabetes mellitus, might be >50%.[1,16]

Although one group of investigators have reported that the number of nontraumatic amputations in people with diabetes mellitus increased in the 5-year period up to 2008,[17] since then, a marked variation in the incidence of amputation across different regions of the UK has been reported.[18] By contrast, a considerable reduction in the incidence of lower extremity amputations in people with diabetes mellitus during a similar period of time was reported in Scotland.[19] Outside the UK, diabetes mellitus is a leading cause of amputation, and has been reviewed extensively elsewhere.[20] In a multicentre study from Europe, infection was confirmed to be a major contributing factor to lower extremity amputation in patients with diabetes mellitus; markers of severity of infection, such as periwound oedema, foul smell and raised C-protein levels, were all found to independently predict amputation.[21] In a study from Iran of patients with diabetes mellitus who presented with foot infections, 45% of participants required local or major amputation.[22] Amputations also frequently result from diabetic foot problems in Asia, and several of the Caribbean islands have some of the highest amputation rates in the world.[23]

Risk factors for foot ulceration

Diabetic peripheral neuropathy

The term diabetic peripheral neuropathy (DPN) is used to describe a variety of symptoms of the nervous system associated with diabetes mellitus. A simple and internationally agreed upon definition is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes".[24]

A diagnosis of DPN cannot be made without a careful clinical examination.[25] DPN is a frequently occurring complication of diabetes mellitus that affects up to 50% of all patients with the disease, and, indeed, is thought to be the most common type of peripheral neuropathy in Western countries.[26] In this Review, we use DPN to refer to the most abundant form of the diabetic neuropathies, which is distal symmetrical, sensorimotor neuropathy.[26] The autonomic nervous system can also be involved in diabetic neuropathy, and peripheral sympathetic autonomic neuropathy of the lower limb is implicated in the development of foot ulcers in patients with diabetes mellitus.[27] Peripheral sympathetic neuropathy is extremely common in patients with diffuse DPN.[25]

Symptoms of DPN can present across a spectrum of severity. At one extreme of this range is a predominantly painful form of the disease with a number of uncomfortable symptoms. Patients can have difficulty describing these symptoms, which manifest differently to normal nociceptive pain that is experienced following, for example, a fall or a burn. These symptoms have been described by patients attending clinics for diabetes care as electrical sensations, stabbing or shooting pain, a burning or freezing sensation in the skin and a dull persistent ache. Painful neuropathic symptoms tend to be exacerbated during the night.[27] These symptoms are of gradual onset and can vary over time.[27]

At the other end of the DPN spectrum, are patients who describe their feet as being numb but who experience few, if any, other symptoms. The numb sensation tends to begin distally in the toes and moves up the lower limb. Patients might also experience allodynia, whereby a non-noxious stimulus can produce an uncomfortable sensation, such as pain, in the neuropathic lower limb. The patient might, therefore, experience extreme discomfort when the bedclothes rub against hyperaesthetic skin in the feet and lower limbs. A careful clinical examination is essential to diagnose DPN and can reveal reduced sensation to large and small fibre stimuli in the feet and lower part of the lower limbs.[28] Some muscle wasting in the small muscles of the feet and, occasionally, the hands might be present, which can also be accompanied by reduced or absent ankle reflexes.[25]

Unsteadiness while standing is also an increasingly recognized symptom of DPN that results from both sensory dysfunction (that is, altered proprioception and reduced joint position sensation) and subsequent adaptations in the motor response. In addition to increasing the risk of trips and falls, unsteadiness is associated with an increased risk of depression.[29]

The underlying pathology and aetiology of DPN are varied and complex; however, both metabolic and vascular factors contribute to the pathogenesis of this complication.[25] Of these factors, hyperglycaemia is the most important. Evidence is accumulating that indicates even patients with impaired glucose tolerance might develop small fibre neuropathy.[30] With the exception of

achieving near-normoglycaemia and the possible use of the antioxidant α-lipoic acid,[25] currently no pathogenetic treatments licensed for use in Western countries to treat DPN.

The most commonly used treatments for symptoms of DPN are aimed at symptomatic relief only, such as antidepressants and anticonvulsants. Consequently, none of the drugs discussed in this Review will have any effect on the natural history of diabetic neuropathy. An in-depth discussion of therapeutic agents used in the management of painful DPN is out of the scope of this Review and has been reviewed extensively elsewhere.[25,27,31]

Treatment of neuropathy

Antidepressants

Tricyclic drugs, such as amitriptyline, have been used since the 1970s as first-line treatments for painful neuropathy.[32] The efficacy of these agents for relieving symptoms of DPN has been confirmed in numerous randomized controlled trials (RCTs) and meta-analyses over the past 35 years.[32] However, use of tricyclic drugs is limited by frequent and predictable adverse effects, such as anti-muscarinic, cardiovascular, central nervous system and endocrine-related symptoms. As an alternative to these drugs, 5-hydroxytryptamine and norepinephrine reuptake inhibitors are increasingly being used, predominantly in the form of duloxetine.[33] In clinical practice, drugs of this class have both antidepressant and analgesic effects, as well as being efficacious. These drugs are also associated with few adverse effects, which might improve tolerability to patients.

Anticonvulsants

Gabapentin is an established treatment for neuropathic pain of varying aetiologies, including DPN, with efficacy having been established by RCTs.[34,35] Pregabalin is also approved for pain relief in patients with DPN, on the basis of results from RCTs.[36] Adverse effects associated with both drugs are similar and adverse interactions with other drugs are minimal. Both pregabalin and duloxetine are recommended by clinical guidelines as a first-line treatment for managing the symptoms of painful diabetic neuropathy.[27,31]

Sympathetic autonomic neuropathy

Peripheral sympathetic autonomic neuropathy is a distal neuropathy that leads to varying degrees of microvascular dysfunction.[37] Clinically, this dysfunction can manifest as a loss of sweating activity in the feet that results in increasingly dry skin and callus formation.[38] Sympathetic denervation can culminate in loss of sympathetic tone resulting in increased blood flow to the foot (in the absence of large vessel peripheral vascular disease).[39] This effect produces a warm but insensate lower limb, and invariably occurs in conjunction with DPN.

Peripheral vascular disease

One the most frequently occurring symptoms of PVD is intermittent claudication, that is, pain from muscle ischaemia after walking.[40] This condition can affect the buttocks, thighs, calves or, rarely, the feet, depending on where in the arterial tree the disease is located. In population-based studies, ~20–25% of people with PVD are asymptomatic for claudication.[8,40] However, approximately one-third of these patients can develop symptoms during a 6-min walk test and even those who manage this test without symptoms have reduced functional performance and calf muscle characteristics compared with individuals without PVD.[41] Interestingly, in one study, one-third of patients who were asymptomatic had an occlusion of a major artery.[42] The most severe symptoms of PVD are associated with critical limb ischaemia (CLI), which can cause pain during rest that requires opiate analgesia for >2 weeks, and results in skin ulcerations or gangrene of the extremities.[43]

Microvascular complications

Poor vision as a consequence of diabetic retinopathy was a predictor of the risk of developing foot ulcers in the Seattle Diabetic Foot Study.[44] Additionally, the high risk of foot ulceration among patients with diabetes mellitus who receive dialysis has been confirmed in a number of studies.[45–47] A temporal association between the start of dialysis and an increased risk of foot ulceration has been reported.[45] Moreover, in another series of studies, undergoing dialysis was found to be an independent risk factor for foot ulceration in patients with diabetes mellitus and the protection against foot ulcers seen in some ethnic populations is lost in patients receiving dialysis.[45–47]

Callus formation, which is a consequence of raised pressure on the foot and sympathetic autonomic neuropathy, is strongly associated with increased risk of foot ulceration.[1] Peripheral oedema, which can compromise local blood flow, has also been associated with an increased risk of foot complications in patients with diabetes mellitus.[48] In a prospective study of risk factors for diabetic foot ulceration, neuropathy, deformity and trauma were the most frequently occurring factors implicated in the development of foot ulcers.[48] Common deformities of the feet include clawing of the toes and problems with the metatarsal heads, which are presumably the result of an imbalance of flexor and extensor motor function in the feet.[48]

Developing foot ulcers

Foot ulceration in patients with diabetes mellitus usually occurs as a result of tissue trauma (which is often unperceived owing to the lack of pain sensation) in the presence of neuropathy and/or PVD. Contrary to widespread assumptions, to our knowledge no direct evidence exists supporting the hypothesis that infection alone, which usually occurs after there has been a break in the skin, leads to foot ulcers. Diabetic neuropathy (usually DPN with autonomic dysfunction) was the most common contributing factor in the development of foot ulcers.[48] However, neuropathy alone does not result in ulceration; rather, ulcerations are the result of a combination of two or more components.[48] National and international diabetes associations

have recommended the principle of the annual review for all patients with diabetes mellitus, whereby each patient is screened at least annually for evidence of diabetic complications.[49]

An annual assessment of the foot is usually performed in the community (for example, in primary care), although this assessment can be carried out in any clinical setting. A taskforce of the American Diabetes Association (ADA) addressed the question of what the annual comprehensive diabetic foot exam should comprise.[49] After taking into consideration evidence from published studies, the ADA taskforce recommended a simple clinical history and examination was all that was required to identify patients at high risk. This annual assessment does not require any expensive equipment or indeed any equipment that runs on an external electrical power source. This simple screening exercise can be carried out accurately, is effective in any health-care setting and can be performed in a few minutes (Box 1).[49] Subsequent to the publication of the ADA taskforce report, additional simple tests have also been developed (Box 2). Unfortunately, no evidence from an RCT has shown that preventative foot care education leads to a reduced incidence of foot ulcers. However, a reduced incidence of foot problems has been reported in observational studies in which education is included in a multidisciplinary teaching approach to diabetes foot care.[50,51]

Box 1 | Key components of the diabetic foot exam

Evidence of past and/or present ulcers

Foot shape
- Prominent metatarsal heads/claw toes
- Hallux valgus
- Muscle wasting
- Charcot deformity

Dermatological
- Callus
- Erythema
- Sweating

Neurological
- 10 g monofilament at four sites on each foot and one of the following:
  - Vibration using 128 Hz tuning fork
  - Pinprick sensation
  - Ankle reflexes
  - Vibration perception threshold

Vascular
- Foot pulses
- Ankle brachial index (if indicated)
- Doppler wave forms

Box 2 | Additional tests to assess diabetic foot conditions

The Ipswich touch test

The Ipswich touch test is based upon the patient's perception of the feel of the touch of another finger. The examiner touches the first, third and fifth toes and asks if the patient can perceive the sense of touch. This test is now a validated procedure and has similar effectiveness to the 10 g monofilament.[101]

VibraTip™

VibraTip™ (McCallan Medical Ltd, UK) is a pocket-sized disposable device that tests the integrity of large-fibre function. When the tip is applied to the toe, the body of the device (itself no longer than 3 cm) is squeezed, which produces vibrations in the tip. VibraTip™ has excellent correlation with the Ipswich touch test, 10 g monofilament and the standard vibration perception threshold test using a neurothesiometer.[102]

Neuropad®

Neuropad® (Miro Verbandstoffe GmBH, Germany) is a simple, noninvasive indicator test to assess peripheral autonomic nervous system integrity by changing colour in response to normal sweating. In the absence of normal sweating (which can occur with sympathetic neuropathy), no colour change occurs. This test has been validated and might also be used as an educational aid to help the patient understand they have a disease, as without the protective sense of pain, appreciating that an abnormality exists is difficult.[103]

Other tests

The most important signs are loss of palpable pulses in the leg, specifically in the femoral, popliteal, dorsalis paedis and posterior tibial arteries. Additional signs of peripheral vascular disease are pallor, especially on elevation, as well as a hyperaemic response on dependency, coolness of the feet, loss of hair and muscle bulk.

Diagnosis

Bedside tests

The ankle pressure and ankle–brachial pressure index (ABPI) is a simple bedside test that provides the ratio of the highest pressure required to occlude Doppler-detected blood flow at the ankle (the highest readings taken at the dorsalis paedis and posterior tibial arteries) compared with that of the brachial artery. The haemodynamic definition of PVD is an ABPI <0.9 and, generally, reduced ABPI is associated with increased disease severity in the arteries of the leg.[8] The ABPI is 95% sensitive in identifying symptomatic patients and is almost 100% specific in identifying healthy individuals.[8] However, in patients with calcified arteries—typically individuals with diabetes mellitus or patients undergoing dialysis—the ABPI can be falsely elevated because occluding the hardened artery is difficult. Consequently, for these individuals, a value >1.4 is considered abnormal. In patients with calcified arteries, the ABPI only has a sensitivity of 50–71% and specificity of 30.0–96.8%.[52]

Toe pressures and the toe–brachial pressure index (TBPI) are often more accurate than the ABPI, especially when the crural vessels are calcified—a problem that is common in patients with diabetes mellitus and/or end-stage renal disease.[52] The method is similar to ABPI with the use of a cuff around the toe to occlude the flow of blood. A TBPI <0.7 is considered abnormal. Microvascular transcutaneous oxygen pressure ($tcPO_2$) is a measure of oxygen supply that is indicative of the local microcirculation and, hence, the degree of ischaemia in the area of interest.[52]

According to the 2007 Trans-Atlantic Inter-Society Consensus Statement (TASC II),[40] in the presence of tissue loss, having an ankle pressure <50–70 mmHg or toe pressure <50 mmHg or $tcPO_2$ <30 mmHg is consistent with the presence of CLI. Each of these bedside tests described above are associated with benefits and limitations. However, in one study, the best predictive value for amputation was toe pressure, specifically, low toe pulse wave amplitude, but $tcPO_2$ measurements added little extra information to guide assessment.[53]

Radiological tests

Duplex ultrasonography can identify arterial lesions on the basis of the anatomical appearance and haemodynamic measures (as determined by peak systolic velocity) to give both anatomical location and degree of stenosis.[54] In pooled meta-analyses, duplex ultrasonography has a sensitivity of 88% and a specificity of 94%, with higher specificity and sensitivity for lesions above the knee than for those below the knee.[53,54]

CT angiography provides imaging of the arterial tree from heart to feet. The accuracy of CT angiography is high, with a pooled sensitivity of 95% and a specificity of 96%, which drops to 91% for tibial vessels.[52,55] The main potential adverse consequences of CT angiography are the radiation doses and nephrotoxicity of the contrast dye administered. Radiation doses range from 7.47 mSv to 13.70 mSv (the average annual background dose of radiation is ~2.00–3.00 mSv).[52] The risk of nephropathy (indicated by an increase in serum levels of creatinine to 25% or 44.20 μmol/l) that is associated with administration of a contrast dye in high-risk patients is ~16.8%; however, overall, <1% of patients undergoing CT angiography require renal replacement therapy.[52]

Magnetic resonance angiography (MRA) is another method that enables the imaging of the whole arterial system and has a pooled sensitivity of 95% and specificity of 97%.[54] Imaging of tibial vessels with MRA is slightly worse than CT angiography, with a sensitivity of 92–95% and specificity of 91–93%.[52] Interestingly, some investigators have suggested that MRA can be as good (if not better) than CT angiography for identifying pedal vessels to receive bypasses in patients with diabetes mellitus who have CLI.[52] MRI avoids use of radiation and is, therefore, fairly safe. However, MRA does have contraindications, specifically with regard to the use of gadolinium-enhanced MRA, with which a small risk of nephrogenic systemic fibrosis is associated in the presence of considerable pre-existing renal dysfunction.[52]

Intra-arterial digital subtraction angiography (DSA) remains the gold-standard for identifying arterial lesions against which all other imaging techniques are compared and provides a complete map of the arterial tree that is easily interpreted and analysed.[52] However, DSA is a 2D lumenogram and, therefore, does not offer the 3D imaging that is associated with techniques such as MRA. In addition, the use of DSA has other disadvantages, including a reduced accuracy of determination of eccentric lesions and, if a lesion is flow limiting, patent distal crural and pedal vessels can be missed.[52] Moreover, the main problems associated with this method are that the procedure is invasive, uses ionizing radiation, complications (such as renal failure) can occur and the technique requires expensive equipment that needs to be operated by skilled staff.[52] The authors of the TASC II statement reported that application of DSA carries a 0.10% risk of severe reaction, a 0.70% risk of complications that require a change of care and is associated with an 0.16% risk of mortality.[40] The UK National Institute for Health and Care Excellence guidelines recommended that arterial duplex ultrasonography should be the first-line imaging modality for determining PVD in patients with diabetes mellitus, contrast-enhanced MRA for patients who require additional imaging before revascularization and that CT angiography should be reserved for patients who are unable to undergo MRA.[8]

Treatment

Medical therapy

Patients with tissue loss and PVD require optimal control of atherosclerotic risk factors to help treat current lesions and aid the durability of revascularization, as well as to prevent the development of lesions and to reduce the risk of cardiovascular morbidity and mortality.[56] Tobacco smoking is the primary risk factor associated with an increased severity of PVD, risk of amputation and mortality and is inversely associated with the durability of revascularization.[57] In addition to advice from physicians, the use of pharmacological aids, such as nicotine replacements, bupropion and varenicline has led to an improvement in the rates of smoking cessation. Other medications that should be prescribed include statins, irrespective of cholesterol levels, and antiplatelet drugs. Risk factors, such as hypertension and diabetes mellitus also need to be optimally controlled.[40,56]

With regard to treatment of CLI, the only drugs that have benefit are parenteral prostanoids (such as iloprost, a drug used to treat pulmonary arterial hypertension), which have shown reductions in pain and ulcer size, as well as improved amputation-free survival at 6 months in RCTs.[58–60] However, treatment with these drugs should be reserved for patients medically unfit for revascularization, or in whom this treatment has previously failed.[40,56] The authors of a Cochrane review identified some benefits that were associated with the use of iloprost. However, the poor quality of many of the available published reports meant that only 20 of 111 potential studies were included in the analysis; additional studies are required in order to draw firm conclusions as to when iloprost is an appropriate medical therapy for diabetic foot complications.[57]

Revascularization

For patients with tissue loss, increased severity of ischaemia is associated with worse outcomes, such as amputation and death;[53] consequently, restoration of skin perfusion is considered to be a critical component of treatment.[40,61] Revascularization can be achieved by endovascular means with balloon angioplasty and stenting, or by open surgical techniques such as endarterectomy and often a bypass around the diseased segment of vessel.[40,41] No RCTs that compare revascularization with no revascularization have been performed to date. Furthermore, the natural history of neuroischaemic ulcers in the diabetic foot has not been well studied. In one study in which 70% of patients with ischaemic limb ulcers also had diabetes mellitus, individuals who did not undergo revascularization had a rate of major amputation of 23% and a rate of wound healing of 53% at 1 year after inclusion in the study.[62] Whereas in another study, in which 50% of the patients with CLI

Table 1 | Pooled patency rates of endovascular interventions*

Lesion location	Lesion type	PTA patency	Stent patency
Iliac artery	Stenosis	65% at 4 years	77% at 4 years
	Occlusion	54% at 4 years	61% at 4 years
Femoropopliteal artery	Stenosis	61% at 3 years	66% at 3 years
	Occlusion	48% at 3 years	64% at 3 years
Infrapopliteal artery	Stenosis and occlusions	74% at 1 year	58% at 1 year

*Comparing PTA with stenting.[40,69] Abbreviation: PTA, percutaneous transluminal angioplasty.

had diabetes mellitus, the amputation rate was 46% at 1 year.[63] This improvement in amputation-free survival between 1996 and 2006 was confirmed in a meta-analysis that focused on trials of patients with CLI who did not have revascularization therapy; however, in this study, the proportion of patients who actually had diabetes mellitus is unclear.[64]

Revascularization of critically ischaemic legs results in increased perfusion after the procedure (as measured by $tcPO_2$) that is associated with a reduced amputation rate.[65] The consequences of bypass failure have also been studied and the risk of amputation was dependent on the initial indication for revascularization, with higher amputation rates associated with tissue loss than with either rest pain or claudication.[66] Another factor that is predictive of amputation risk is the period of time from bypass to occlusion. Decreased rates of amputation are associated with an increased time that the bypass of the lesion has being functional.[66] One possible explanation for this inverse association is that, especially with tissue loss, if the ulcer had healed, experiencing bypass failure was not as harmful, owing to the procedure having contributed to healing the lesion.[66] In a comparison of a conservative first-line strategy, using drug therapy alone (with analgesia and prostaglandins), with revascularization in patients with CLI early revascularization resulted in improved clinical outcomes.[67] Notably, patients with diabetes mellitus needed more re-interventions than patients with CLI without diabetes mellitus, as a consequence of increased rates of restenosis. However, if an aggressive surveillance and re-intervention protocol was followed, patients with diabetes mellitus performed as well as patients without diabetes mellitus.[67]

Endovascular therapy

Endovascular techniques use the principle of traversing a wire through and beyond the diseased segment of artery, which is then dilated with either a balloon or a stent. The technique is performed percutaneously and is, therefore, normally possible to execute under local anaesthetic, which enables a rapid recovery from the procedure. In general, angioplasty works less well if the treated vessel is near the foot or if the lesion is long or occluded—these anatomical factors lead to poorer outcomes.[40] Many patients with diabetes mellitus have long tibial occlusions, which result in considerable challenges for the success of endovascular techniques.[68]

The patency of endovascular therapy to treat an occlusion or stenosis is >50% (Table 1). However, these data are the pooled results from several sources in which many patients with claudication and a variable number of patients with diabetes mellitus were included.[40,69] Consequently, these numbers probably overestimate outcomes in patients with diabetes mellitus and CLI (Table 1). The role of different balloons and stents for endovascular intervention is beyond the scope of this article, but, in general, the extra cost of a stent is justified in patients with flow-limiting dissections after angioplasty, in whom angioplasty fails to establish an adequate flow channel and possibly those patients with occlusive vascular disease.[40,69,70]

Surgery

The optimal surgical techniques for the treatment of CLI are endarterectomy (to correct an atherosclerotic plaque that narrows or occludes the vessel) and bypass surgery that uses either a vein or prosthetic material to bypass the lesion.[40] These techniques normally require the administration of either general or local anaesthesia, which is associated with at least a few days in hospital and several weeks required to heal the surgical scar. The further from the heart the distal anastomosis is located and the longer the length of bypass, the lower the patency at 5 years (Figure 1).[40] Notably, prosthetic bypasses performed below the knee have much worse patency than vein bypasses.[40] Patients with diabetes mellitus typically have tibial vessel disease, and consequently distal bypasses taken from the popliteal artery to arteries at, or beyond, the ankle are often required. In a meta-analysis, 63% primary and 71% secondary patency rates were recorded at 5 years for patients treated with vein bypass surgery.[71]

Surgery versus endovascular intervention

Few high-quality RCTs that compare surgical methods with endovascular revascularization have been performed. Important considerations when deciding on an appropriate treatment include early efficacy, long-term durability and morbidity and mortality associated with the procedure. Consequently, endovascular treatment is the preferred option if a lesion is easy to treat and likely to remain in the patient, especially if comorbidities make general anaesthesia medically unsafe for the patient. The TASC II guidelines advise that for patients with diseased iliac and femoropopliteal arteries, stenoses and short occlusions are best treated with endovascular techniques, whereas surgery is preferred for long occlusions or extensive multisegment disease (that is, where the disease affects a number of different segments in one or more arteries).[40] However, as endovascular techniques improve, the use of these methods is rapidly increasing compared with open surgeries.[72]

The BASIL trial is the only large RCT to compare surgery with endovascular intervention in cases where genuine doubt existed regarding the best treatment option for the patient.[73] Findings from this trial suggested that for lesions in the infrainguinal artery (and if the patient had a good vein for bypass and their life

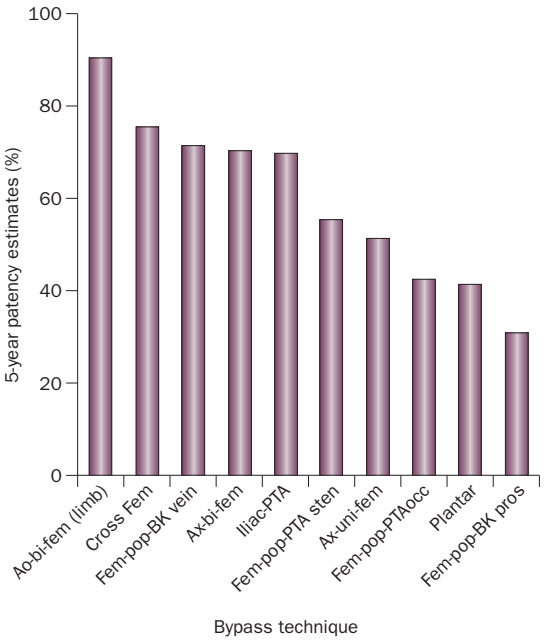

Figure 1 | 5-year patency estimates for surgical bypass in critical limb ischaemia. Patency can be as high as 87% for Ao-bi-fem bypass but as low as 33% for fem-pop BK bypass. Abbrevations: Ao-bi-fem, aortobifemoral bypass; Ax-bi-fem, axillobifemoral bypass; Ax-uni-fem, axillounifemoral bypass; BK, below knee; Fem-pop, femoropopliteal; pros, prosthetic; PTA, percutaneous transluminal angioplasty. Reproduced with permission from Elsevier © Norgren, L. *et al.* Inter-society consensus for the management of peripheral arterial disease (TASC II). *J. Vasc. Surg.* **45** (Suppl.), S5–S67 (2007).[40]

expectancy was >2 years), surgery was better than endovascular revascularization.[73] If the patient has no suitable vein or a life expectancy of <2 years, then endovascular revascularization should be attempted. However, in the BASIL trial only ~40% of the participants had diabetes mellitus.[73] Notably, endovascular techniques have advanced considerably since this study was conducted. Furthermore, controversy surrounds the finding that failed endovascular revascularizations might impair success of future bypass methods.[67,73]

In the past few years, a focus has been directed toward angiosomal perfusion to areas of tissue loss.[74–76] This technique is based on the three tibial arteries (that is, peroneal, anterior and posterior) supplying different parts of the foot, therefore, attempts to revascularize need to focus on supplying the vessel that best feeds the area where tissue loss has occurred, especially in the feet of patients with diabetes mellitus.[74–76] Indeed, some evidence suggests that wound healing and limb salvage is improved[64] with this method, especially for angioplasty,[75,76] although valid criticisms, such as the retrospective nature of these studies, have been raised.[77]

A comparison of healing between surgical and endovascular revascularization techniques revealed that for large wounds, surgical bypass seems to achieve better wound healing than endovascular techniques, in terms of the proportion of patients healed and with a trend for quicker healing.[78] Notably, in this group of patients, the presumption that bypass is dangerous while angioplasty is safe has been challenged by the authors of a review in which 30-day mortality was 1.4% for bypass surgery, but mortality was still substantial at 0.5% after revascularization.[79] Furthermore, true success of treatment is not merely measured by limb salvage, but by healing of all wounds (including surgical scars), which is a slow process with a median time of 190 days, even for bypass.[80]

The choice of technique is partly dependent on the physical fitness of the patient, the anatomy of the lesion, its angiosomal relationship to the ulcer to be treated and the expertise available. In addition, the forthcoming outcomes of the BASIL-2 trial might help to clarify matters for patients with an occlusion or stenosis in the infrapopliteal arteries.[81]

Management of diabetic foot ulcers

Debridement

Hyperkeratotic tissue develops on the plantar surface of the foot as a result of shear pressure. Regular debridement of the excess keratin that forms the callus provides a reduction in abnormally elevated plantar pressures and reduces the risk of ulceration.[82] Removal of this overlying layer, and any necrotic tissue underneath, enables drainage of fluid from the ulcer so that it can begin to heal naturally from the base.[82] Wounds extending to bone and infected soft tissues require deep and aggressive debridement to achieve removal of nonviable tissue and provide drainage of purulent discharge. Complete excision can considerably reduce the number of days taken to heal compared with ulcers managed conservatively.[82]

Offloading

Offloading is the recommended first-choice treatment option for diabetic foot ulcers.[83] The aim of offloading is to reduce pressure on the foot by decreasing the weight-bearing load and redistributing the pressure over an increased area of the foot. Devices to promote offloading include removable or nonremovable casts, orthotic devices (such as the patella–tendon weight-bearing orthosis) and custom fabricated shoes and insoles.[84]

The 'total contact cast' is the most effective offloading device and has become the gold-standard in Europe and the USA.[85] Healing times are considerably shorter when total contact casting is used compared with other methods of offloading.[85] The total contact cast is nonremovable and, therefore, the patient must wear the cast at all times. However, in a study examining the activity patterns of patients with removable casts, poor compliance with treatment was observed and participants wore the casts for only a minority of steps per day.[86]

Wound dressings

The minimum requirements for a diabetic foot ulcer wound dressing are the protection from external contaminants and absorption of exudate while maintaining an environment that promotes healing. Many dressings are available that offer increasingly advanced methods of improving wound

Table 2 | Wound management products for diabetic foot complications

Dressing type	Description	Considerations for use
Hydrocolloid	Facilitates rehydration and autolytic debridement Used for dry, sloughy, necrotic wounds Promotes granulation	Avoid for infected wounds Requires twice weekly change
Hydrogels	Donates liquid to dry wounds and absorbs exudates Used for dry, sloughy wounds Promotes autolytic debridement	Avoid for infected wounds
Silver	Antimicrobial	Avoid if sensitive to silver
Vapour-permeable	Provides a moist healing environment Used for mild exudating wounds	Avoid for heavily exudating wounds
Foam dressing	Used as primary or secondary cover Used for light and heavy exudating wounds	Remove if dressing stained
Odour absorbent	Absorbs odour Malodorous	Avoid if sensitive to silver
Larval therapy	Debridement, promote granulation Used for heavily sloughy necrotic wounds	Stop treatment in response to increase in pain
Alginate	Haemostat Used for heavy exudating wounds	Blockage Loose fibres
Skin substitutes	Living skin Used for obstinate wounds	Avoid for colonized or infected wounds
Iodine	Antibacterial Used for exudating wounds	Sensitivity to iodine Presence of renal or thyroid diseases
Honey	Antimicrobial Used for sloughy necrotic wounds Autolytic debridement	Use only medical grade honey

healing (Table 2). Moist dressings reportedly provide an environment conducive to wound healing by maintaining optimal levels of moisture to encourage cell migration and matrix formation. However, no evidence from RCTs exists that indicates these dressings are more effective in wound healing than 'dry' dressings.[87] Similarly, dressings impregnated with silver have not been shown to be more effective in treating diabetic foot ulcers in RCTs than dressings for treating any other type of wound.[88] Other studies comparing different types of dressings have also been unable to identify evidence to support efficacy in healing diabetic foot ulcers.[89]

Negative pressure wound therapy

The use of negative pressure wound therapy is becoming more widespread in the clinical setting and involves the removal of wound fluid through a sealed vacuum.[90] Increased rates of healing of diabetic foot ulcers and increased rates of wound closure have been associated with application of this therapy.[91] Improved perfusion, and promotion of formation of granulated tissue, are two of the reported benefits of applying negative pressure to wounds.[92]

Growth factors and skin substitutes

Wound healing involves a complex interaction of growth factors, including platelet-derived growth factor.[93] The potential application of growth factors to aid wound healing in diabetic foot ulcers is an area of growing therapeutic interest.[94] Becaplermin is a recombinant platelet-derived growth factor available as an ointment and has shown some benefit for foot ulcers.[95] Granulocyte colony-stimulating factor has been reported to improve resolution of infection in a pilot study of this condition.[96] In another study, treatment with granulocyte colony-stimulating factor resulted in reduced amputation rates.[97] However, substantiation of these findings is required. Bioengineered skin and human dermis tissues are new types of biologically active implants for ulcers and contain human fibroblasts that deliver growth factors and components of the extracellular matrix.[98] However, the evidence on many of these expensive therapies is poor and large-scale RCTs are still required.

Multidisciplinary team input

The effective management of diabetic foot complications relies on achieving stability across multiple aspects of diabetes mellitus care. Glycaemic control, kidney function, visual system, blood pressure and intact cognition are aspects of the disease that considerably influence prognosis. Comprehensive and effective management can only be achieved through multidisciplinary care, across many different care providers.[99]

Patients who require treatment from a specialist diabetes foot care team need a structured management plan to contend with the multiple comorbidities and complications associated with diabetes mellitus. A specialist foot care team for patients with diabetes mellitus should include a diabetologist, podiatrist, specialist nurse and a surgeon with a thorough understanding of foot function (who can be a podiatric, orthopaedic, vascular or general surgeon).[51]

When multidisciplinary care is delivered, improved outcomes, including reduced incidence of minor and

major amputations, have been demonstrated.[100] The investigators of one study directly compared outcomes associated with care delivered by an established multidisciplinary diabetes mellitus team with care delivered in a hospital that lacked a designated diabetes mellitus team. In this study, patients treated by the diabetes mellitus multidisciplinary team underwent substantially fewer major amputations (4.7%) than those treated without multidisciplinary team input (21.7%).[100] Mortality during hospitalization was also considerably reduced, with a mortality rate of 2.5% being associated with care from a multidisciplinary team compared with 9.4% for patients not treated by a multidisciplinary team.[100]

Conclusions

Diabetic foot complications arise from the complex interactions between microvascular and macrovascular irregularities. Infection, peripheral neuropathy and/or ischaemia are major contributors to the development of foot lesions in patients with diabetes mellitus. The absence of pain makes the foot highly vulnerable to external influences, such as ill-fitting footwear, foreign objects and thermal injury, which can drive rapid development of ulceration. Although prevention is the best strategy for managing foot complications in patients with diabetes mellitus, if a foot lesion does occur, a combination of treatment methods are available.

1. Boulton, A. J. The pathway to foot ulceration in diabetes. *Med. Clin. North Am.* **97**, 775–790 (2013).
2. Singh, N., Armstrong, D. G. & Lipsky, B. A. Preventing foot ulcers in patients with diabetes. *JAMA* **293**, 217–228 (2005).
3. Kerr, M., Rayman, G. & Jeffcoate, W. J. Cost of diabetic foot disease to the National Health Service in England. *Diabetic Med.* **31**, 1498–1504 (2014).
4. Armstrong, D. G. *et al.* Mind the gap: disparity between research funding and costs of care for diabetic foot ulcers. *Diabetes Care* **36**, 1815–1817 (2013).
5. Armstrong, D. G., Wrobel, J. & Robbins, J. M. Are diabetes-related wounds worse than cancer? *Int. Wound J.* **4**, 286–287 (2007).
6. Lavery, L. A., Hunt, N. A., Ndip, A., Lavery, D. C. & Boulton, A. J. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. *Diabetes Care* **33**, 2365–2369 (2010).
7. Buse, J. B. *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American heart association and the American diabetes association. *Diabetes Care* **115**, 114–126 (2007).
8. NICE. *Lower limb peripheral arterial disease: diagnosis and management. NICE guidelines [CG147]* [online], http://guidance.nice.org.uk/CG147 (2012).
9. Jeffcoate, W. J. & Harding, K. Diabetic foot ulcers. *Lancet* **361**, 1545–1551 (2003).
10. Abbott, C. A. *et al.* The North West Diabetes Foot Care Study: Incidence of and risk factors for new diabetic foot ulceration in a community-based cohort. *Diabetic Med.* **19**, 377–384 (2002).
11. Muller, I. S. *et al.* Foot ulceration and lower limb amputation in type 2 diabetic patients in Dutch primary health care. *Diabetes Care* **25**, 570–574 (2002).
12. Abbott, C. A. *et al.* Foot ulcer risk is lower in South Asian and African-Caribbean compared to European diabetic patients in the UK: the North-West diabetes foot care study. *Diabetes Care* **28**, 1869–1875 (2005).
13. Monteiro-Soares, M. *et al.* Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab. Res. Rev.* **28**, 574–600 (2012).
14. Leese, G., Stang, D. & McKnight, J. A national strategic approach to diabetic foot disease in Scotland: a changing culture. *Br. J. Diabetes Vasc. Dis.* **11**, 69–73 (2011).
15. Margolis, D. J. & Jeffcoate, W. J. Epidemiology of foot ulceration and amputation. *Med. Clin. N. Amer.* **97**, 7791–7805 (2013).
16. Boulton, A. J. M. in *Evidence Based Management of Diabetes* (eds Giten, V. & Busen, J.) 367–382 (TFM Publishing, 2012).
17. Vamos, E. P., Bottle, A. & Edmonds, M. E. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. *Diabetes Care* **33**, 2592–2597 (2010).
18. Holman, N., Young, R. J. & Jeffcoate, W. J. Variation in the recorded incidence of amputation of the lower limb in England. *Diabetologia* **55**, 1919–1925 (2012).
19. Kennon, B., Leese, G. P. & Cochrane, L. Reduced incidence of lower-extremity amputations in people with diabetes in Scotland: a nationwide study. *Diabetes Care* **35**, 2588–2590 (2012).
20. Chevreul, K., Berg Brigham, K. & Bouché, C. The burden and treatment of diabetes in France. *Global Health* **10**, 6 (2014).
21. Pickwell, K. *et al.* Predictors of lower extremity amputation in patients with an infected diabetic foot ulcer. *Diabetes Care* **38**, 852–857 (2015).
22. Hadadi, A. *et al.* Diabetic foot: infections and outcomes in Iranian admitted patients. *Jundishapur J. Microbiol.* **7**, e11680 (2014).
23. Boulton, A. J. M., Vileikyte, L., Ragnarson-Tennvall, G. & Apelqvist, J. The global burden of diabetic foot disease. *Lancet* **366**, 1721–1726 (2005).
24. Boulton, A. J. M., Gries, J. A. & Jervell, J. A. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. Special Report. *Diabetic Med.* **15**, 508–514 (1998).
25. Boulton, A. J. M., Malik, R. A., Arezzo, J. & Sosenko, J. M. Diabetic somatic neuropathies. *Diabetes Care* **27**, 1458–1486 (2004).
26. Dyck, P. J. *et al.* The prevalence by staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* **43**, 817–824 (1993).
27. Tesfaye, S., Boulton, A. J. M. & Dickenson, A. H. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care* **36**, 2456–2465 (2013).
28. Dyck, P. J. *et al.* Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab. Res. Rev.* **27**, 620 (2011).
29. Vileikyte, L. *et al.* Foot ulcer risk is lower in South Asian and African-Caribbean compared to European diabetic patients in the UK. The North-West diabetes foot care study. *Diabetes Care* **28**, 1869–1875 (2005).
30. Smith, A. G. & Singleton, J. R. Impaired glucose tolerance and neuropathy. *Neurologist* **14**, 23–29 (2008).
31. Tesfaye, S. *et al.* Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab. Res. Rev.* **12**, 65–68 (2011).
32. Davis, J. L. *et al.* Peripheral diabetic neuropathy treated with amitryptiline and fluphenazine. *JAMA* **238**, 2291–2292 (1977).
33. Sultan, A., Gaskell, H., Derry, S. & Moore, R. A. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: a systematic review of randomised trials. *BMC Neurol.* **29**, 1471–2377 (2008).
34. Caraceni, A. *et al.* Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. *J. Clin. Oncol.* **22**, 2909–2917 (2004).
35. Backonja, M. *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* **280**, 1831–1836 (1998).
36. Freeman, R., Durso-Decruz, E. & Emir, B. Efficacy, safety and tolerability of pregabalin treatment for painful peripheral neuropathy: findings from seven randomised, controlled trials across a range of doses. *Diabetes Care* **31**, 1448–1454 (2008).
37. Morris, S. J., Shore, A. C. & Tooke, J. E. Responses of the skin microcirculation to acetylcholine and sodium nitroprusside in patients with non-insulin dependent diabetes mellitus. *Diabetologia* **38**, 1337–1344 (1995).
38. Ryder, R. E. *et al.* Autonomic dennervation may be a prerequisite of diabetic neuropathic foot ulceration. *Diabetic Med.* **7**, 726–730 (1990).
39. LeFrandt, J. D. *et al.* Sympathetic mediated vasomotion and skin capillary permeability in diabetic patients with peripheral neuropathy. *Diabetologia* **246**, 40–47 (2003).
40. Norgren, L. *et al.* Inter-society consensus for the management of peripheral arterial disease (TASC II). *J. Vasc. Surg.* **45** (Suppl.), S5–S67 (2007).
41. McDermott, M. M. *et al.* Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation* **117**, 2484–2491 (2008).
42. Fowkes F. G. *et al.* Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int. J. Epidemiol.* **20**, 384–392 (1991).

43. Becker, F. *et al.* Chapter I: Definitions, epidemiology, clinical presentation and prognosis. *Eur. J. Vasc. Endovasc. Surg.* **42** (Suppl. 2), S4–S12 (2011).
44. Boyko, E. J., Ahroni, J. H., Cohen, V., Nelson, K. M. & Heagerty, P. J. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* **29**, 1202–1207 (2006).
45. Game, F. L., Chipchase, S. Y., Hubbard, R., Burden, R. P. & Jeffcoate, W. J. Temporal association between the incidence of foot ulceration and the start of dialysis in diabetes mellitus. *Nephrol. Dial. Transplant*. **21**, 3207–3210 (2006).
46. Ndip, A. *et al.* Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. *Diabetes Care* **33**, 1811–1816 (2010).
47. Ndip, A. *et al.* High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy. *Diabetes Care* **33**, 878–880 (2010).
48. Reiber, G. E. *et al.* Causal pathways for incident lower extremity ulcers in patients with diabetes from two settings. *Diabetes Care* **22**, 157–162 (1999).
49. Boulton, A. J. M. *et al.* Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* **31**, 1679–1685 (2008).
50. Krishnan, S., Nash, F., Baker, N., Fowler, D. & Rayman, G. Reduction in diabetic amputations over eleven years in a defined UK population: benefits of multi-disciplinary team work and continuous prospective audit. *Diabetes Care* **31**, 99–101 (2008).
51. Kuehn, B. M. Prompt response, multi-disciplinary care: key to reducing diabetic foot amputation. *JAMA* **308**, 19–20 (2012).
52. Cao, P. *et al.* Chapter II: Diagnostic methods. *Eur. J. Vasc. Endovasc. Surg.* **42** (Suppl. 2), S13–S32 (2011).
53. Carter, S. A. & Tate, R. B. The relationship of the transcutaneous oxygen tension, pulse waves and systolic pressures to the risk for limb amputation in patients with peripheral arterial disease and skin ulcers or gangrene. *Int. Angiol*. **25**, 67–72 (2006).
54. Collins, R. *et al.* Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. *BMJ* **334**, 1257 (2007).
55. Met, R., Bipat, S., Legemate, D. A., Reekers, J. A. & Koelemay, M. J. W. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* **301**, 415–424 (2009).
56. Diehm, N. *et al.* Chapter III: Management of cardiovascular risk factors and medical therapy. *Eur. J. Vasc. Endovasc. Surg.* **42** (Suppl. 2), S33–S42 (2011).
57. Ruffolo, A. A. J., Romano, M. & Ciapponi, A. Prostanoids for critical limb ischaemia. *Cochrane Database of Systematic Reviews* Issue 1. Art. No.: CD006544 http://dx.doi.org/10.1002/14651858.CD006544.pub2.
58. Brock, F. E. *et al.* Iloprost in the treatment of ischemic tissue lesions in diabetics. Results of a placebo-controlled multicenter study with a stable prostacyclin derivative. *Schweiz. Med. Wochenschr.* **120**, 1477–1482 (1990).
59. Altstaedt, H. O. *et al.* Treatment of patients with peripheral arterial occlusive disease Fontaine stage IV with intravenous iloprost and PGE1: a randomized open controlled study. *Prostaglandins Leukot. Essent. Fatty Acids* **49**, 573–578 (1993).
60. Stiegler, H. *et al.* Placebo controlled, double-blind study of the effectiveness of i.v. prostaglandin E1 in diabetic patients with stage IV arterial occlusive disease [German]. *Vasa. Suppl*. **35**, 164–166 (1992).
61. Bakker, K. *et al.* Practical guidelines on the management and prevention of the diabetic foot. *Diabetes Metab. Res. Rev.* **28**, 225–231 (2011).
62. Marston, W. A. *et al.* Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J. Vasc. Surg.* **44**, 108–114 (2006).
63. Lepäntalo, M. & Mätzke, S. Outcome of unreconstructed chronic critical leg ischaemia. *Eur. J. Vasc. Endovasc. Surg.* **11**, 153–157 (1996).
64. Benoit, E., O'Donnell, T. F., Kitsios, G. D. & Iafrati, M. D. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J. Vasc. Surg.* **55**, 781–789 (2012).
65. Faglia, E. *et al.* Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. *Eur. J. Vasc. Endovasc. Surg.* **32**, 484–490 (2006).
66. Baldwin, Z. K. *et al.* Limb salvage after infrainguinal bypass graft failure. *J. Vasc. Surg.* **39**, 951–957 (2004).
67. Dick, F. *et al.* Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. *J. Vasc. Surg.* **45**, 751–761 (2007).
68. Kalish, J. & Hamdan, A. Management of diabetic foot problems. *J. Vasc. Surg.* **51**, 476–486 (2010).
69. Wu, R. *et al.* Percutaneous transluminal angioplasty versus primary stenting in infrapopliteal arterial disease: a meta-analysis of randomized trials. *J. Vasc. Surg.* **59**, 1711–1720 (2014).
70. Bekken, J. A., Jongsma, H., de Vries, J. P. & Fioole, B. Self-expanding stents and aortoiliac occlusive disease: a review of the literature. *Med. Devices* **7**, 99–105 (2014).
71. Albers, M., Romiti, M., Brochado-Neto, F. C., De Luccia, N. & Pereira, C. A. B. Meta-analysis of popliteal-to-distal vein bypass grafts for critical ischemia. *J. Vasc. Surg.* **43**, 498–503 (2006).
72. Skrepnek, G. H., Armstrong, D. G. & Mills, J. L. Open bypass and endovascular procedures among diabetic foot ulcer cases in the United States from 2001 to 2010. *J. Vasc. Surg.* **60**, 1255–1264 (2014).
73. Adam, D. J. *et al.* Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* **366**, 1925–1934 (2005).
74. Bosanquet, D. C., Glasbey, J. C., Williams, I. M. & Twine, C. P. Systematic review and meta-analysis of direct versus indirect angiosomal revascularisation of infrapopliteal arteries. *Eur. J. Vasc. Endovasc. Surg.* **48**, 88–97 (2014).
75. Iida, O. *et al.* Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. *J. Vasc. Surg.* **55**, 363–370 (2012).
76. Söderström, M. *et al.* Angiosome-targeted infrapopliteal endovascular revascularization for treatment of diabetic foot ulcers. *J. Vasc. Surg.* **57**, 427–435 (2013).
77. Sumpio, B. E. *et al.* Clinical implications of the angiosome model in peripheral vascular disease. *J. Vasc. Surg.* **58**, 814–826 (2013).
78. Neville, R. F. & Sidawy, A. N. Surgical bypass: when is it best and do angiosomes play a role? *Semin. Vasc. Surg.* **25**, 102–107 (2012).
79. Hinchliffe, R. & Andros, G. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. *Diabetes Metab. Res. Rev.* **28** (Suppl. 1), 179–217 (2012).
80. Söderström, M., Arvela, E., Albäck, A., Aho, P. S. & Lepäntalo, M. Healing of ischaemic tissue lesions after infrainguinal bypass surgery for critical leg ischaemia. *Eur. J. Vasc. Endovasc. Surg.* **36**, 90–95 (2008).
81. University of Birmingham *BASIL-2 Trial* [online], http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/Basil-2/index.aspx (2015).
82. Pitei, D. L., Foster, A. & Edmonds, M. The effect of regular callus removal on foot pressures. *J. Foot Ankle Surg.* **38**, 251–255 (1999).
83. Armstrong, D. G. *et al.* Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomised controlled trial. *Diabetes Care* **28**, 551–554 (2005).
84. Bus, S. A., Haspels, R. & Busch-Westbroek, T. E. Evaluation and optimisation of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis. *Diabetes Care* **34**, 1595–1600 (2011).
85. Katz, I. A. *et al.* A randomised controlled trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* **28**, 555–559 (2005).
86. Armstrong, D. G. *et al.* Activity patterns of patients with diabetic foot ulceration: patients with active ulceration may not adhere to standard pressure off-loading regimen. *Diabetes Care* **26**, 2595–2597 (2003).
87. Dumville, J. C., Deschpande, S., O'Meara, S. & Speak, K. Hydrocolloid dressings for healing diabetic foot ulcers. *Cochrane Database of Systematic Reviews* Issue 8. Art. No.: CD009099 http://dx.doi.org/10.1002/14651858.CD009099.pub3.
88. Jude, E. B., Apelqvist, J., Spraul, M. & Martini, J. Silver dressing study group. Prospective randomised controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressing in non-ischameic diabetic foot ulcers. *Diabetic Med*. **24**, 280–288 (2007).
89. Jeffcoate, W. J. *et al.* Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. *Health Technol. Assess*. **13**, 1–86 (2009).
90. Saxena, V. *et al.* Vacuum assisted closure: microdeformations of wound and cell proliferation. *Plast. Reconstr. Surg.* **114**, 1086–1098 (2004).
91. Armstrong, D. G. & Lavery, L. A. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* **366**, 1704–1710 (2005).
92. Krug, E. *et al.* Evidence-based recommendations for the use of negative pressure wound therapy in traumatic wounds and reconstructive surgery: steps towards an international consensus. *Injury* **42** (Suppl. 1), S1–S12 (2011).
93. Werner, S. & Grose, R. Regulation of wound healing by growth factors and cytokines. *Physiol. Rev.* **83**, 835–870 (2003).

94. Henshaw, F. R., Boughton, P., Lo, L., McLennan, S. V. & Twigg, S. M. Topically applied connective tissue growth factor/CCN2 improves diabetic preclinical cutaneous wound healing: potential role for CTGF in human diabetic foot ulcer healing. *J. Diabetes Res.* http://dx.doi.org/10.1155/2015/236238.
95. Pappanas, N. & Maltosze, E. Becaplermin is form recombinant platelet-derived growth factor available as an ointment and has shown some benefit. *Clin. Interv. Aging* **3**, 233–240 (2008).
96. Dignani, M. C. *et al.* Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: a pilot study. *Leukemia* **11**, 1621–1630 (1997).
97. Cruciani, M., Lipsky, B. A., Mengoli, C. & de Lalla, F. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* **28**, 454–460 (2005).
98. Choi, J. S., Kim, J. D., Yoon, H. S. & Cho, Y. W. Full-thickness skin wound healing using human placenta-derived extracellular matrix containing bioactive molecules. *Tissue Eng. Part A* **19**, 329–339 (2013).
99. Antoline, C., Kramer, A. & Roth, M. Implementation and methodology of a multidisciplinary disease-state-management program for comprehensive diabetes care. *Permanenta J.* **15**, 43–48 (2011).
100. Krishnan, S., Nash, F., Baker, N., Fowler, D. & Rayman, G. Reduction in diabetic amputations over eleven years in a defined UK population: benefits of multi-disciplinary team work and continuous prospective audit. *Diabetes Care* **31**, 99–101 (2008).
101. Rayman, G. *et al.* The Ipswich Touch Test: a simple and novel method to identify inpatients with diabetes at risk of foot ulceration. *Diabetes Care* **34**, 1517–1518 (2011).
102. Bowling, F. L. *et al.* A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting. *Diabetic Med.* **29**, 1550–1552 (2012).
103. Papanas, N. *et al.* Neuropad: A simple new non-invasive sweat indicator test for the diagnosis of diabetic neuropathy. *Diabetic Med.* **30**, 525–534 (2013).

Author contributions

All authors contributed equally to researching the data for the article, discussion of content, writing the article and reviewing and/or editing the manuscript.