Neuropathy and foot problems in diabetes

SG Gilbey MD FRCP, Consultant Physician,
Leeds Teaching Hospitals, Leeds

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Introduction

The cardiovascular system (considered in another article in this series) bears the brunt of diabetic complications. The kidney, another important target organ, is susceptible to both microvascular and macrovascular disease. This article concentrates both on neuropathy as a cause of multisystem disease in diabetes and on diabetic foot disease as a condition where prompt, appropriate action by a non-diabetologist can prevent major morbidity.

The diabetic foot

Epidemiology

Foot ulcers occur in 5–10% of the diabetic population, with an annual incidence of 2–3% and a 3% lifetime risk of amputation. Neuropathy and peripheral vascular disease both contribute to foot disease. Diabetic patients undergoing amputation have a one-year mortality of 11–41%.

How to reduce the incidence of foot ulceration and amputation

Improve the control of blood glucose and cardiovascular risk factors. Prospective studies in type 1[1] and type 2 diabetes[2] have confirmed the importance of blood glucose control. The United Kingdom Prospective Diabetes Study showed that:

- a 1% reduction in haemoglobin A1c from any baseline level reduced the risk of amputation or death from peripheral vascular disease by 43%,[3] and
- there is a 16% decrease in amputation or death from vascular disease for every 1 mmHg reduction in systolic blood pressure.[4]

In the Heart Protection Study,[5] random allocation to simvastatin reduced vascular events (coronary events, strokes, revascularisation) in diabetic patients by 22% (p <0.0001) with a marginally significant reduction in the much smaller number of patients developing peripheral macrovascular complications (arterial surgery, angioplasty, amputation or foot ulcers).

Improve the organisation of foot care for all patients with diabetes and define t hose at risk of foot ulceration (Table 1). All diabetic patients should have their feet examined at least once a year and be given simple advice on foot care, footwear and ulcer prevention. Assessment of the following can identify high risk patients[6] who need to be under regular review by a community or hospital podiatrist:

- peripheral vascular disease (impalpable pulses or reduced ankle/brachial plexus systolic blood pressure index)
- neuropathy (assessment of light touch using a 10 g neurofilament fibre (Fig 1), and
- foot deformity.

Patients with foot disease benefit from attending a diabetic foot clinic where podiatrists, orthotic shoe fitters and diabetologists work together and have access to vascular and orthopaedic surgeons.

Who needs urgent referral or admission?

Any patients with foot ulceration should be referred for assessment (Table 2) and

Table 1. Risk factors for diabetic foot ulceration.

Risk factor	Clinical features
Neuropathy:	
• sensory	Reduced light touch sensation Reduced temperature sensation
• motor	Small muscle wasting leading to foot deformity/high foot pressure
• autonomic	Reduced sweating Dry skin Altered small vessel regulation
Peripheral vascular disease	Diabetic pattern of distal atherosclerosis
Other risk factors Diabetic nephropathy Smoking Hyperlipidaemia Hypertension Poor vision Poor foot care Old age	

Fig 1. A 10 g monofilament for testing sensation.

Table 2. Assessment of a diabetic foot ulcer.

Site, size and depth of ulcer	Clinical observation
Evidence of cellulitis, spreading infection, osteomyelitis	Clinical observation X-ray MRI
Evidence of neuropathy and deformity	Clinical observation Sensory testing ?Autonomic function
Evidence of vascular insufficiency	Clinical observation Ankle/brachial blood pressure index (abnormal if <0.8; may be obscured by vascular calcification) Angiography (MR angiography if contraindicated)

MRI = magnetic resonance imaging.

Table 3. Leeds antibiotic policy for diabetic foot ulceration (courtesy of Dr C Amery).

If clinical suspicion of infection (erythema, raised CRP)	Swab all ulcers (deep as possible) Bone scrapings if possible
Outpatients	Amoxycillin + flucloxacillin Clindamycin if penicillin allergy
If osteomyelitis suspected (admit acute cases)	Clindamycin + ciprofloxacin (12 weeks)
Inpatients	iv benzylpenicillin + flucloxacillin (+ metronidazole if significant infection) iv clindamycin + oral ciprofloxacin if penicillin allergy
If osteomyelitis suspected	iv flucloxacillin, oral ciprofloxacin + metronidazole iv clindamycin + oral ciprofloxacin if penicillin allergy
Review antibiotic choice with swab result	

CRP = C-reactive protein; iv = intravenous.

Key Points

The life time risk of amputation for a diabetic patient is 3%

Long-term control of blood glucose and blood pressure has been shown to reduce the risk of macro- and microvascular diabetic complications in type 1 and type 2 diabetes

All diabetic patients should have regular foot review and foot care advice

Diabetic foot clinics reduce the risk of ulceration leading to amputation

The acute Charcot foot needs urgent admission and immobilisation

Current therapy for diabetic painful neuropathy is disappointingly ineffective

Symptomatic diabetic autonomic neuropathy is rare

KEY WORDS: amputation, Charcot foot, diabetes, foot disease, neuropathy, peripheral vascular disease

intervention in a foot clinic. Urgent referral is indicated by markers of significant infection (local erythema, pain, systemic unwellness), increasing size or depth of ulcer. Hospital admission is indicated for:

- administration of intravenous antibiotics for severe ulceration and infection including osteomyelitis (Table 3)
- urgent investigations (X-ray, magnetic resonance imaging), angiography) with a view to intervention (Fig 2(a) and (b)): local debridement/ foot surgery, angioplasty, vascular reconstruction, amputation.

Intervention for foot ulceration includes:

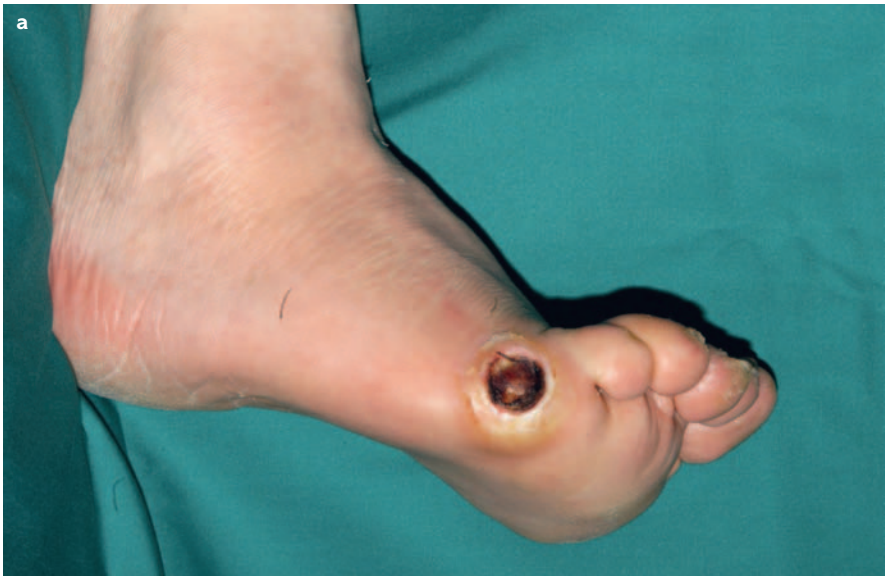
- local treatment (degranulation, removal of dead tissue, application of maggots)
- antibiotics
- surgery/debridement/skin flap to enable healing
- osteotomy to relieve high pressure areas, and
- revascularisation/amputation.

The Charcot foot

The Charcot foot occurs in patients with a relatively long duration of diabetes (type 1 or type 2) and poor diabetes control. In one series of 1,000 diabetic patients, 26% were at risk of foot ulceration and 0.4% had a Charcot foot.[7] Patients usually have severe peripheral sensory neuropathy in the presence of good peripheral circulation. The pathophysiology of the acute Charcot foot is unclear. Abnormal local vascular responses, similar to those in reflex sympathetic dystrophy and due to sympathetic neuropathy, may lead to a hypervascular response to local trauma, local bone resorption and osteopenia, setting up a vicious circle of local fracture and inflammation.[8] This in turn results in foot deformities and a high risk of ulceration.

The acute Charcot foot (Fig 3) presents with pain and swelling. Failure to diagnose this will result in persistent weight bearing by the patient and a cycle of continuing bone damage. The main differential diagnosis is infection. Patients in whom clinical and radiological examination leave the diagnosis in doubt may have to be treated with antibiotics 'blindly'. Any patient who appears to be developing a Charcot foot should be referred urgently, with hospital admission indicated if the index of suspicion is reasonably high.

Treatment (Table 4) involves immobilisation for a period of weeks, with subsequent use of full contact casts and Walker boots to reduce pressure on the foot. Because of the apparent role of



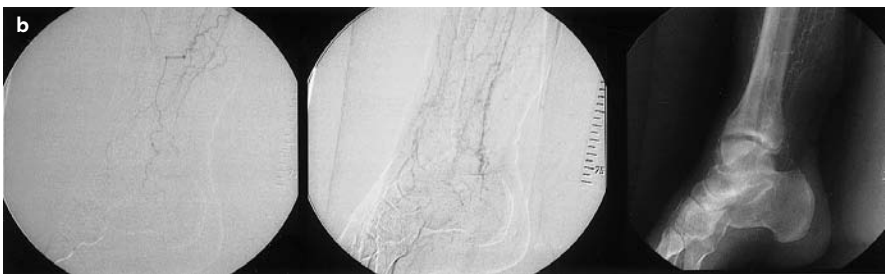


Fig 2. Diabetic foot ulcer: (a) the foot shows the typical 'claw foot' deformity with prominent metatarsal heads secondary to neuropathy and small muscle wasting; **(b)** the angiogram shows diffuse, distal arterial disease with no prospect for reconstruction.

osteopenia and fracture, bisphosphonates have been used to 'stabilise' bone turnover and accelerate recovery from the acute phase. One placebo-controlled study showed that a single dose of pamidronate could reduce pain and local inflammation but did not alter the natural history of the neuroarthropathic process.[9]

The chronic Charcot foot is painless, deformed and vulnerable to repeated ulceration. Increasingly, orthopaedic intervention (including surgery) is used to reduce both deformity and pressure areas.

Diabetic neuropathy

A simple classification of diabetic neuropathy is summarised in Table 5. There is a multifactorial aetiology. Prolonged hyperglycaemia leads to local metabolic changes, all of which may contribute to neuropathy:

- sorbitol accumulation
- myoinositol depletion[10]
- glycosylation of local tissue, and
- local damage to small vessels within the nerve bundle (microvascular disease).[11]

Experimental attempts to reverse metabolic changes and improve clinical disease using aldose reductase inhibitors have been unsuccessful. The only treatment for which there is unequivocal evidence of benefit for nerve function and some evidence of benefit for neuropathic symptoms is improved diabetic control.

Peripheral sensory neuropathy

Sensory neuropathy in diabetes is irreversible and symmetrical ('glove and

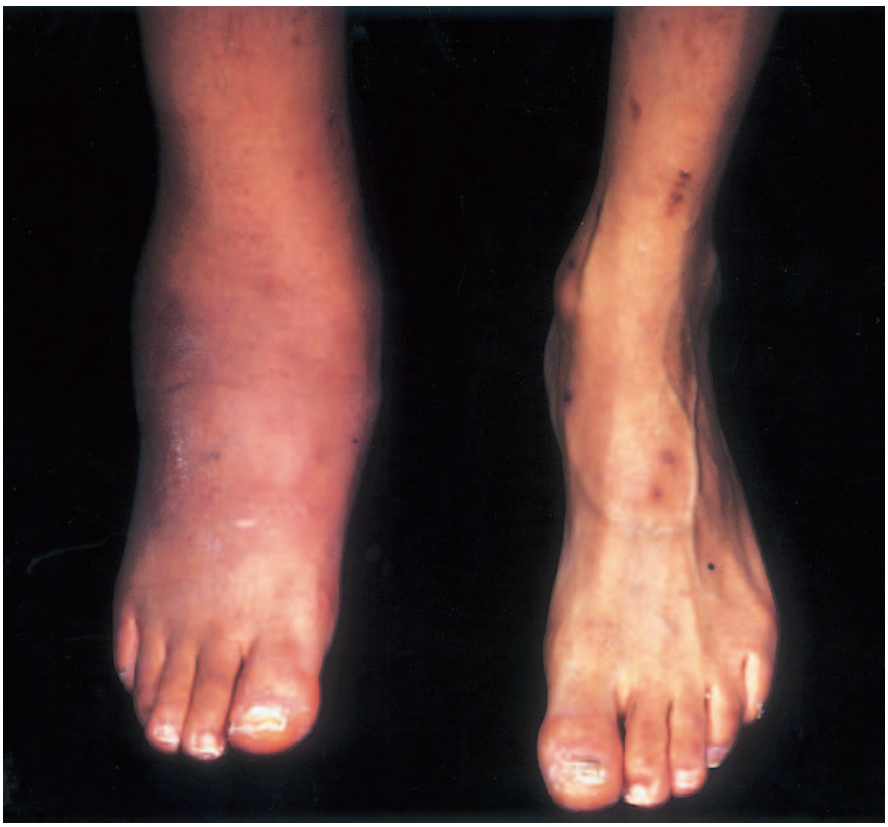


Fig 3. An acute Charcot foot. The right foot is swollen and painful, requiring immobilisation and relief of weight bearing.

Table 4. The Charcot foot.

Phase	Symptoms	Findings	Management
Acute phase	Pain Swelling	Raised CRP Erythema Fractures/joint subluxation Increased bony disorganisation Increased blood flow Osteopenia	Immobilisation/off-loading Analgesia Glucose control
Chronic phase	Foot deformity Analgesia	Chronic bony changes Increased foot pressures Increased ulcer risk Increased risk contralateralCharcot	Foot care advice Bespoke footwear Regular podiatric review Surgery to relieve pressure areas (selected cases)

CRP = C-reactive protein.

stocking'). It preferentially affects small fibres mediating pain and temperature, particularly in the early phase. Longer nerves are especially vulnerable – hence the predilection for neuropathy in the diabetic foot, which is in turn the anatomical site most vulnerable to mechanical damage. Clinical symptoms of neuropathy have been found in up to 50% of diabetic patients[12] and up to 11% have chronic pain. Patients with type 2 diabetes may present with established sensory neuropathy, presumably due to a prolonged period of undiagnosed diabetes.

Painful neuropathy

Symptomatic neuropathy can be an acute presenting feature of diabetes ('hyperglycaemic' neuropathy, usually self-limiting) or follow a period of rapid improvement of diabetic control for reasons that remain unclear. 'Diabetic neuropathic cachexia' is a syndrome of severe painful neuropathy associated with depression, anorexia and weight loss, with gradual resolution over a period of months.

Neuropathic pain ranges from mild discomfort to severe, distressing, unrelenting symptoms, including:

- burning
- shooting, lancinating
- 'walking on marbles'
- paraesthesia/hyperaesthesia
- aching/cramping, and
- nocturnal exacerbation/contact dysaesthesia (allodynia).

Loss of sleep due to nocturnal symptoms is a major problem and exacerbates the disruption to quality of life. Chronic pain may persist for years.

The variety of treatments available (Table 6) indicates how difficult diabetic pain is to treat.[13] Patients need to be made aware of the difficulty of treatment. A combined approach with a pain specialist service may be helpful.

Motor neuropathy and mononeuropathies

Diabetic amyotrophy (or proximal motor neuropathy) is a predominantly motor neuropathy causing pain, weakness and atrophy affecting the pelvic girdle and thigh musculature. The diagnosis can be made clinically and with nerve conduction studies. Management includes improved diabetes control and analgesia. The usual natural history is gradual resolution over 6–18 months. The major differential diagnosis is a spinal problem causing nerve root compression.

Mononeuropathies can affect thoracic nerve roots (thoracic radiculopathy) and cranial nerves.

The pathophysiology of motor neuropathy and mononeuropathies in diabetes is unclear but most likely ischaemic. The natural history is resolution with time. Management is symptomatic with optimisation of diabetic control.

Table 5. A classification of diabetic neuropathies.

Chronic symmetric	Distal sensory (may have chronic painful symptoms) Sensorimotor (associated with mild motor weakness) Autonomic
Acute/reversible	Acute painful neuropathy (often associated with weight loss) Diabetic amyotrophy (painful neuropathy with muscle wasting) Acute focal neuropathy (eg cranial, radiculopathy)
Compression neuropathies (ulnar, median nerves)	Ulnar, median nerves

Table 6. Treatment of confirmed painful diabetic neuropathy.

First-line	Improve diabetic control Tricyclic antidepressants (particularly if sleep disturbance) Substitute gabapentin if tricyclics unsuccessful
Second-line	Alternative anti-epileptic agents (carbamazepine, phenytoin) Antiarrhythmic agents (eg intravenous lignocaine) Topical treatments (capsaicin, Op-site) Topical nitrates (under investigation) Narcotic analgesics Transcutaneous electrical nerve stimulation Sympathectomy

Nerve entrapment syndromes of any type are more common in diabetic than non-diabetic people for reasons that remain unclear.

Autonomic neuropathy

Symptomatic autonomic neuropathy is rare in diabetic patients. It is so often accompanied by overt somatic neuropathy that the absence of peripheral neuropathy should prompt a search for another cause for symptoms eg adrenocortical insufficiency in diabetic patients presenting with postural hypotension and vomiting. On the other hand, subtle autonomic dysfunction may play a significant part in the pathophysiology of cardiovascular complications of diabetes. An extreme example is diabetic patients with symptomatic autonomic neuropathy who have a small but significant risk of sudden death thought to be attributable to cardiac arrhythmias.[14]

Clinical features of autonomic neuropathy and their management (Tables 7 and 8)

Cardiovascular autonomic dysfunction

Patients with established diabetic autonomic neuropathy have a fixed, increased heart rate due to loss of vagal tone and cardiovascular reflexes. This is the basis of most simple measurements of autonomic function in diabetes.

Postural hypotension

Postural hypotension, a late feature of diabetic autonomic neuropathy, is defined as a fall in systolic blood pressure of over 30 mmHg on standing, with symptoms. It may take 2–3 minutes for the blood pressure drop to manifest itself.

Gastroparesis

Abnormalities of gastric function are found in 30–50% of patients with long-standing diabetes.[15] Symptomatic gastroparesis with recurrent vomiting can be intractable. Hyperglycaemia has a major influence on gastric emptying so a

Table 7. Clinical features of diabetic autonomic neuropathy.

System	Clinical features
Cardiovascular	Fixed unresponsive heart rate Symptomatic postural hypotension (postural fall of systolic BP >30 mmHg Neuropathic oedema Cardiorespiratory arrest
Gastrointestinal	Diarrhoea/constipation Gastroparesis Gustatory sweating
Genitourinary	Bladder paresis Erectile dysfunction (multifactorial) Retrograde ejaculation

Table 8. Clinical management of autonomic neuropathic symptoms.

Symptoms	Clinical management
Postural hypotension	Mineralocorticoids Sympathomimetic agents (ephedrine, midodrine) Partial beta-agonists (pindolol) Prostaglandin synthetase inhibitors Octreotide (constricts splanchnic bed) Desmopressin acetate
Gastroparesis	Correct hyperglycaemia Domperidone Metoclopramide Erythromycin Percutaneous jejunostomy if required for nutrition Surgery rarely useful
Diabetic diarrhoea	Exclude other causes (coeliac disease, metformin, pancreatic insufficiency) Conventional antidiarrhoeal agents Tetracyclines (presumed bacterial overgrowth) Clonidine Octreotide

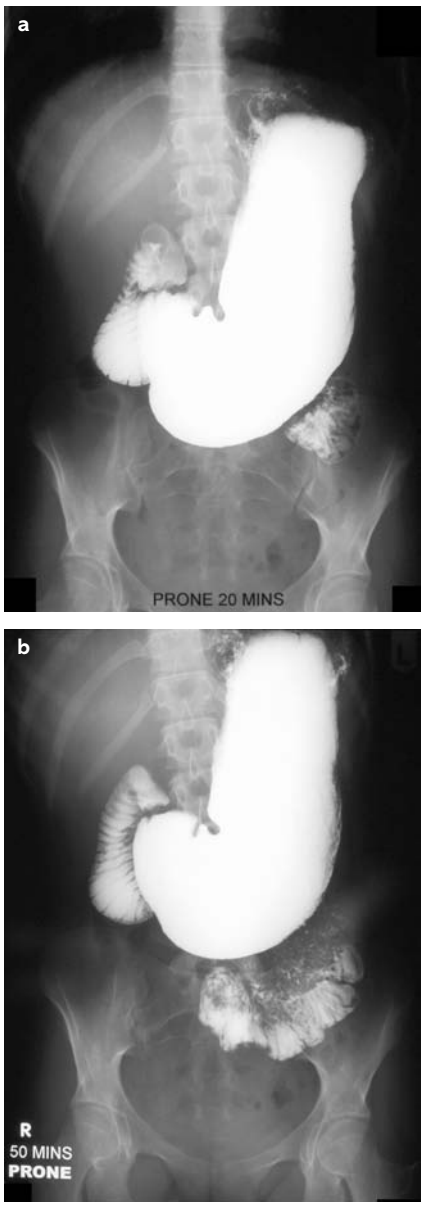


Fig 4. Delayed gastric emptying – diabetic gastroparesis. Symptoms improved dramatically with improved diabetic control.

priority is to optimise glycaemic control. Investigations confirm grossly delayed gastric emptying (Fig 4).

Diabetic diarrhoea and constipation

Patients with symptomatic autonomic neuropathy can present dramatically with profuse watery diarrhoea including faecal incontinence. This is often interspersed with prolonged episodes of constipation. Other causes of diarrhoea need to be excluded, including:

- pancreatic pathology
- coeliac disease (2–6% prevalence in type 1 diabetes[16]), and
- metformin therapy.

Treatment is with antidiarrhoeal agents and, in some patients, short courses of antibiotics (eg tetracycline) which can relieve diarrhoea by treating bacterial overgrowth.

Bladder symptoms

Bladder symptoms include impaired bladder sensation, inability to void urine and a sense of inadequate bladder emptying. Investigations show an increased residual urine volume post-micturition. Treatment is by behavioural and pharmacological techniques to improve bladder emptying and, if necessary, self-catheterisation to reduce the risk of infection.

Erectile dysfunction

Causes of erectile dysfunction include autonomic dysfunction and vascular disease. Treatment has been revolutionised by phosphodiesterase inhibitors such as sildenafil, reducing the need for a panoply of alternative treatments.

When should autonomic function tests be arranged?

The main value of autonomic function tests is to confirm that a patient with somatic neuropathy who is suspected of autonomic symptoms does have abnormal autonomic function. Most tests are based on parasympathetic cardiovascular reflexes because these are easily quantified and correlate well with other tests such as peripheral sweating abnormalities. Postural hypotension is easily measured but it is a late feature of symptomatic neuropathy (see above).

Conflict of interest

None.

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