Recent advances in the diagnosis and management of diabetic neuropathy

The World Health Organisation estimated that in the year 2000, 150 million people had diabetes mellitus, and it is predicted that this number will rise to 366 million by the year 2030. Neuropathy is a common complication of diabetes and is characterised by a progressive loss of peripheral nerve fibres. There are a number of manifestations including both mono- and polyneuropathies. In the diabetic foot, distal sensory polyneuropathy is seen most commonly. However, motor and autonomic fibres may also be involved and combined neuropathies frequently occur. The development of a neuropathy is linked to poor glycaemic control over many years and it increases in frequency with both age and the duration of diabetes.

Epidemiology
The epidemiology and natural history of diabetic neuropathy remain poorly defined. A number of studies have indicated that the prevalence of neuropathy is approximately 30% among diabetic patients attending hospital while lower rates closer to 20% are seen in population-based samples. Among the elderly, the prevalence may be as high as 50%. It varies from 14% to 63% depending upon the type of population studied and the criteria used to define diabetic neuropathy. In the EURODIAB IDDM Complication Study which included 3250 patients, the overall prevalence of neuropathy in 16 European countries was 28%. In the Rochester Diabetic Neuropathy Study, it affected almost 60% of subjects although it was symptomatic only in about 15%.

Causation
Despite much intensive research, the pathophysiology remains unclear. The principal theories are of microvascular disease leading to neural hypoxia, and the direct effects of hyperglycaemia on neuronal metabolism. Recently, attempts to unify these two theories have demonstrated abnormalities in nitric oxide metabolism, resulting in altered perineural blood flow and nerve damage. Longitudinal data from the Rochester Study supported the contention that the duration and severity of exposure to hyperglycaemia influenced the severity of the neuropathy. To date no treatment which prevents or reverses its development and progression has been identified. Recently, however, numerous competing or parallel pathological pathways have been shown to intersect and complement each other, thus illuminating potential pharmacological targets. Current research on diabetic neuropathy is focused on oxidative stress, advanced glycation-end products, protein kinase C and the polyol pathway.

Clinical features
Chronic diabetic sensorimotor polyneuropathy is the most common manifestation of diabetic neuropathy. It occurs in both type 1 and type 2 diabetes and is more frequent with increasing age and duration of diabetes. The symptoms may be intermittent and of similar character, but with less intensity than those of a painful neuropathy. In one study, it was reported that 30% of type 1 diabetic patients of both genders and 36% of male and 40% of female type 2 diabetic patients had neuropathic symptoms. However, 10% of males and 12% of females in the non-diabetic population reported similar symptoms.

Acute sensory neuropathy is rare, tends to occur after a period of metabolic instability and is characterised by pain, but with few clinical signs. As in acute sensory neuropathy, painful symptoms of chronic diabetic sensorimotor polyneuropathy tend to be more pronounced at night, but in addition, patients may experience ‘negative symptoms’ such as numbness or a ‘dead’ feeling in the feet. Patients often find it difficult to describe the symptoms. There may be unsteadiness because of disturbed proprioception and abnormal muscle sensory function. Such unsteadiness has been quantified and may result in falls and in Charcot’s neuroarthropathy.
On clinical examination, there is usually a symmetrical sensory loss to all modalities in a stocking distribution. In severe cases this may extend well above the ankle and may involve the hands. The knee and ankle reflexes may be reduced or absent. Motor weakness is unusual, although small muscle wasting in the feet and hands may be seen in advanced cases. Any pronounced motor signs should raise the possibility of a non-diabetic neuropathy, especially if they are asymmetrical. In more severe cases, patients may have a positive Romberg’s sign.

Since diabetic polyneuropathy is often accompanied by distal (sympathetic) autonomic changes, there may be clinical signs of autonomic dysfunction including warm dry skin, in the absence of peripheral vascular disease, and plantar callosities under pressure-bearing areas. The ‘at-risk’ foot for neuropathic ulceration may also have a high arch (pes cavus) and clawing of the toes. However, it must be emphasised that all patients with diabetic polyneuropathy with or without obvious foot deformities must be considered as being at risk of complications.

**Symptomatic treatment of neuropathy**

Most treatments have no effect on the natural history of the neuropathy, which is of progressive loss of nerve function. The initial management of patients with a symptomatic neuropathy is summarised in Table I.

**Control of hyperglycaemia.** A number of small open-label uncontrolled studies have suggested that achieving stable nearly normoglycaemic control is helpful in the management of painful neuropathic symptoms. In one such study, patients with a painful neuropathy were treated by a continuous subcutaneous infusion of insulin for four months.

As well as relief from neuropathic symptoms, improvement was noted in quantitative sensory testing and electrophysiological investigations. Improvement of glycaemic control was assessed by measurement of glycated haemoglobin as well as regular monitoring of blood glucose at home. In another study, when patients with painful neuropathy were compared with those with painless neuropathy, those with symptoms of pain had poorer control, more excursions to hyper- and hypoglycaemic levels and a greater fluctuation in the level of blood glucose. The stability of glycaemic control may be as important as the absolute level of blood glucose.

**Pharmacotherapy.** A large number of therapeutic agents have been used for painful symptoms.

**Tricyclic drugs.** Several randomised clinical trials have supported the use of these agents in the management of neuropathic pain. The mechanisms by which these relieve pain include inhibition of re-uptake of norepinephrine and/or serotonin at the synapses of central descending pain control systems and antagonism of N-methyl-D-aspartate receptors, which mediate hyperalgesia and allodynia. Although these agents remain the first line treatment for symptomatic neuropathy in most centres, their use is restricted because of the frequency and severity of side-effects.

Most experience has been achieved with amitriptyline and imipramine. Desipramine is another useful drug which may be better tolerated than amitriptyline in many patients. The major problem with these agents is the frequency of side-effects, which are predictable. Their severity is attributed to their relative affinities for muscarinic, histaminic, and α1-adrenergic receptors.

**Selective serotonin-re-uptake inhibitors.** These inhibit presynaptic re-uptake of serotonin. Studies suggest that treatment with paroxetine, but not fluoxetine, is associated with considerable relief from pain. Similarly, citalopram was confirmed to be efficacious in relieving neuropathic pain, but was less effective than imipramine. In general, selective serotonin re-uptake inhibitors are considered to be better tolerated, but less effective, than tricyclic agents, and they should not be considered for monotherapy of diabetic neuropathy.

**Anticonvulsants.** These have been used in the management of neuropathic pain for many years. Gabapentin is an adjuvant anticonvulsant which is emerging as a first-line agent for the treatment of painful neuropathy. In a large controlled trial, significant relief from pain and reduced sleep disturbance were reported. It appears to be well tolerated, with dizziness and somnolence being the most commonly reported adverse events. Although overall efficacy and safety profiles appear to be favourable, larger long-term studies are needed to define its place as a major treatment for diabetic neuropathy.

Pregabalin is an analogue with similar structure and actions to gabapentin. In the largest study reported thus far involving patients with painful diabetic neuropathy, it was significantly superior to a placebo in improving pain.

**Lamotrigine.** An anti-epileptic agent with at least two antinociceptive properties. Eisenberg et al confirmed the efficacy of this agent in patients with neuropathic pain.

**Anti-arrhythmics.** Mexilitine is a class-B anti-arrhythmic agent. Its efficacy in neuropathic pain has been confirmed in controlled trials. Regular ECG monitoring is necessary, and long-term use cannot be recommended.

**Other agents.** Duloxetine is an inhibitor of the re-uptake of 5-hydroxytryptamine and norepinephrine and has recently been approved by the Food and Drug Administration for the treatment of neuropathic pain. However, at the time of

**Table I. Initial management of symptomatic neuropathy**

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<td>1</td>
<td>Exclude non-diabetic causes including:</td>
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<td>Malignancy (e.g. bronchogenic carcinoma)</td>
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<td>Toxic (e.g. alcohol)</td>
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<td>Infective (e.g. HIV infection)</td>
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<td></td>
<td>Iatrogenic (e.g. isoniazid, vinca alkaloids)</td>
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<td>Medication-related (chemotherapy, HIV treatment)</td>
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<td>2</td>
<td>Explanation, support and practical measures (e.g. bed cradle to lift bedclothes off hyperaesthetic skin)</td>
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<td>3</td>
<td>Assess level of blood-glucose control profiles</td>
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<td>4</td>
<td>Aim for optimal stable control</td>
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<td>5</td>
<td>Consider pharmacological treatment</td>
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writing, the evidence of the efficacy of this agent has only been published in abstract form.\textsuperscript{31} Tramadol is a centrally-acting, synthetic non-narcotic analgesic. Its efficacy in the management of neuropathic pain was confirmed in a randomised control trial.\textsuperscript{32} Similarly, two randomised trials have demonstrated the efficacy of controlled-release oxycodone for neuropathic pain in diabetes.\textsuperscript{33,34} Opioids may be considered as further treatment for patients failing to respond to non-opioid medication.

**Treatment of Charcot foot**

Charcot neuroarthropathy is a non-infective arthropathy in a well-perfused, insensitive foot. Its treatment depends on the stage at which it is diagnosed. In the acute phase, there is evidence that off-loading the affected foot using a plaster cast is most effective in reducing activity of the disease, which can be monitored by the difference in skin temperature between the active and the contralateral foot. The wearing of a cast should continue until the swelling and hyperaemia have resolved and the skin temperature differential is 1˚C or less, at which time custom-moulded shoes with insoles should be worn. Bisphosphonates are potent inhibitors of activation of osteoclasts and have been shown by measurement of bone turnover markers to be useful in reducing the activity of acute Charcot neuroarthropathy.\textsuperscript{35} Patients with a history of neuroarthropathy are at high risk of future problems in the foot, and careful follow-up is mandatory.

**Neuropathic foot ulceration**

Diabetic ulceration of the foot represents a major global medical, social and economic problem. It is the commonest major end-point of diabetic complications. Diabetic neuropathy and peripheral vascular disease are the main aetiological factors in foot ulceration and may act alone, together, or in combination with other factors such as microvascular disease, biomechanical abnormalities, limited joint mobility and increased susceptibility to infection. While more than 5% of diabetic patients have a history of foot ulceration, the cumulative lifetime incidence may be as high as 25%.\textsuperscript{36} Foot problems in diabetic patients account for more hospital admissions than any other long-term complications of diabetes and also result in increasing morbidity and mortality.\textsuperscript{37,38} The ‘diabetic foot syndrome’ encompasses a number of pathologies, including neuropathy, peripheral vascular disease, neuroarthropathy, foot ulceration, osteomyelitis and the potentially preventable end-point of amputation.\textsuperscript{39} Patients with a diabetic foot can also have many diabetic complications and a multidisciplinary approach is usually necessary.

There are ethnic differences in both the incidence of diabetic ulceration and amputation with both being less common in patients from the Indian subcontinent living in the United Kingdom. Ulceration results from the interaction of several contributory factors, the most important of which is neuropathy.

**Causal pathways to foot ulceration**

Ulceration rarely results from a single pathology. It is the interaction of contributory causes which leads to the breakdown of the foot at risk.\textsuperscript{35} The neuropathic foot, for example, does not spontaneously ulcerate. It is the combination of insensitivity and either extrinsic factors, e.g. walking barefoot and stepping on a sharp object, or simply wearing ill-fitted shoes, or intrinsic factors such as diminished sensation and the development of a callosity which progresses to an ulcer on walking. Neuropathy is the most significant pathology in the pathway to ulceration.\textsuperscript{40}

**Neuropathy.** The association between both somatic and autonomic neuropathy and foot ulceration has been recognised for many years.\textsuperscript{41} It is only in the last decade that prospective follow-up studies have confirmed the causative role of somatic neuropathy.\textsuperscript{42-44} Patients with sensory loss have an increased risk of developing foot ulcers of up to sevenfold, compared with non-neuropathic diabetic patients. Unsteadiness has been increasingly recognised as a troublesome symptom of peripheral neuropathy, presumably secondary to proprioceptive loss. The relationship between sway, postural instability and foot ulceration has been confirmed.\textsuperscript{45,46}

Peripheral autonomic (sympathetic) dysfunction results in dry skin and, in the absence of peripheral vascular disease, a warm foot with distended dorsal veins of the foot. This may pose problems in terms of the education of the patient since there is strong lay belief that all foot problems result from vascular disease. Thus, patients may find it difficult to accept that their warm but pain-free feet are at considerable risk of unperceived trauma and subsequent ulceration.\textsuperscript{47}

In practice, peripheral neuropathy can easily be documented by simple clinical examination of the function of large fibres, such as loss of vibration perception using a 128-Hz tuning fork and of small fibres, by hot-cold rods and/or pin-prick sensation, in the feet, and assessment of the ankle reflexes.\textsuperscript{42,48} A composite score compromising these clinical indices, the modified neuropathy disability score, has been shown to be useful in the prediction of those at risk of future ulceration.\textsuperscript{41} The 10-g monofilament, used to test perception of pressure, is often employed to assess the risk status of the feet of diabetic patients.\textsuperscript{49} Although simple to perform, care must be taken to ensure that the filaments can deliver a 10-g force when used.\textsuperscript{50} Moreover, it has also been suggested that this may not be the most sensitive test.\textsuperscript{51} For clinical research electrophysiological measurements such as the conduction velocity in the peroneal nerve have been shown to be an excellent surrogate end-point for foot ulceration in trials of agents which may influence the natural history of neuropathy.\textsuperscript{52}

**Peripheral vascular disease.** Atherosclerotic disease is probably present, at least in a subclinical form, in most patients with diabetes of long duration. Vascular disease is responsible for up to 70% of deaths in type-2 diabetics. In addition, the premenopausal protection from vascular disease is
lost in female diabetic patients and peripheral vascular disease may be 20 times more common in diabetics.53

Peripheral ischaemia resulting from proximal arterial disease was given as a cause in the pathway to ulceration in 35% of patients in a two-centre study of causal pathways.54 A recent comparative study of peripheral arterial disease in diabetic and non-diabetic patients has confirmed that diabetic patients have more distal disease and a poorer outcome with respect to amputation and mortality.55 The ischaemic foot is red, dry and often neuropathic. It is therefore susceptible to pressure from footwear.  

**Other risk factors.** Several studies have confirmed that foot ulceration is most common in those with a past history of ulceration or amputation, and also in patients with a poor social background. In many diabetic foot clinics more than 50% of patients with new foot ulcers have a past history of similar problems.56 The presence of foot deformity, particularly claw toes and prominent metatarsal heads, is a proven risk factor for ulceration.41,57 Similarly, in one cross-sectional study accumulation of plantar callus was associated with a 77-fold increase in risk. However, in the follow-up of the same group of patients, plantar ulcers only occurred at the sites of callus in neuropathic feet, representing a significant increase in risk.58

Other risk factors include the presence of other microvascular complications, increasing duration of diabetes, increase in plantar foot pressures and peripheral oedema.

**Prevention of foot ulceration**
Prevention of foot ulcers among those at risk is pivotal if the high incidence of ulcers is to be reduced, especially since more than 80% of amputations are preceded by ulcers. Unfortunately, a systematic review of studies on education in preventative foot care did not confirm the usefulness of education.59 There is, however, a suggestion that education and regular podiatric care may result in earlier presentation when ulcers develop.60 It has been shown that providing all diabetic patients who are at risk of developing foot ulcers with adequate prevention can be a cost-effective and even cost-saving strategy.61

Most studies describe on physical factors which contribute to the development of ulcers. As discussed by Vileikyte

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**Fig. 1**
Diagram of causal pathways to foot ulceration emphasising the key role of the patient in the prevention of ulcers (spheres and arrows).
there have been very few studies of psychosocial factors in regard to ulcers. It appears that the behaviour of the patients is driven not by the abstract designation of being ‘at-risk’, but by their own perception of their risks. Thus, if patients do not believe that a foot ulcer lies on the path from neuropathy to amputation, they are unlikely to follow educational advice on how to reduce the risk of ulcers. It is clear that research in this area is urgently required. A pathway to foot ulceration including areas where psychosocial factors are relevant is presented in Figure 1.

Foot examination. The most important aspect of diagnosing the foot at risk of ulceration is to examine it regularly in detail for evidence of neuropathy, vascular disease, deformities, plantar callus, oedema and other risk factors. A simple foot-pressure mat such as the PressureStat system (Foot Logic, New York, New York) can help to identify areas of high pressure and pressure maps of the foot, in which areas of higher pressure appear darker, may be used to educate patients about the risk of subsequent ulceration.

Summary and key parts
1. Diabetic sensorimotor polyneuropathy is common (20% to 30% of diabetics).
2. Up to 50% of patients with diabetic sensorimotor polyneuropathy are asymptomatic.
3. It cannot be diagnosed by history alone.
4. It is essential to examine the feet carefully and regularly.
5. The presence of unilateral heat and swelling in a neuropathic diabetic patient should be presumed to be due to acute Charcot neuropathy until proven otherwise.

References


