Theories, types and treatments of diabetic neuropathy

An understanding of the complex aetiology of diabetic neuropathy, the commonest neuropathy in the developed world, aids management of this condition, and helps to avoid potentially very disabling complications.

Diabetes mellitus is a huge public health issue affecting 246 million people worldwide which, with current growing rates of obesity, could double by 2030. From this we can estimate that 20–30 million people have symptomatic diabetic peripheral neuropathy and we know that diabetic peripheral neuropathy is the commonest cause of peripheral neuropathy in developed countries. This review will discuss the prevalence of diabetic peripheral neuropathy, theories regarding pathophysiology as these relate to possible therapies, and the remarkable range of clinical manifestations and their individual managements. In some studies, insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus groups are described, in others type 1 and type 2 diabetes mellitus are referred to, and this article will use whichever convention is used in the particular research paper.

Prevalence

The frequency of diabetic peripheral neuropathy is uncertain as there is a lack of well-constructed prospective studies using validated assessment methods, although it is clear that frequency varies according to how it is diagnosed. Jean Pirart (Pirart, 1977) from Brussels followed more than 4000 patients over 25 years from 1947 and found, using simple clinical examination only, prevalence was 7.5% at diagnosis and almost 50% after 25 years.

More sophisticated studies have used a combination of clinical examination and investigation to diagnose diabetic peripheral neuropathy, although results are very similar: the Rochester study (Dyck et al, 1993) found the prevalence to be 54% in insulin-dependent diabetes mellitus and 45% in non-insulin-dependent diabetes mellitus, with 15% and 13% respectively being symptomatic. What seems fairly clear is that prevalence increases with time and with poor glycaemic control. Severe neuropathy occasionally develops just months after diagnosis in young adults with poorly controlled type 1 diabetes mellitus, although it must be remembered that diagnosis does not necessarily correlate with disease onset, and that a degree of hyperglycaemia may have been present for significantly longer.

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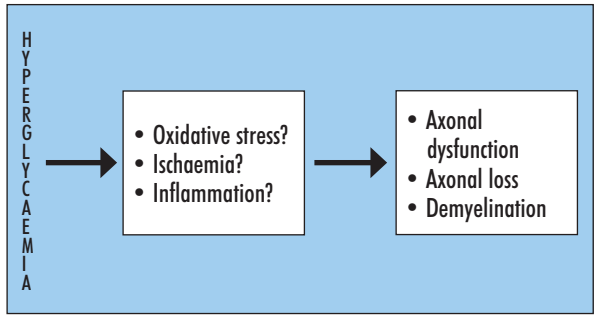
Aetiology

As the question marks in *Figure 1* illustrate, we remain uncertain about the cause of diabetic peripheral neuropathy. Much research in the past has focussed on possible single biochemical mechanisms, mostly neat hypotheses linked with the possible development of therapies. Many of the theories are based on animal models of diabetes, none of which truly reproduce the changes seen in humans. These lines of research have not, to date, been very useful with regards to the development of effective drugs. The current consensus is that it is likely that several molecular mechanisms downstream of hyperglycaemia are responsible, although different types of neuropathy may have different aetiologies.

Longstanding hyperglycaemia does seem to be the culprit. In the Diabetes Control and Complications Trial (The Diabetes Control and Complications Trial Research Group, 1993) a 60% reduction in the occurrence of clinical diabetic peripheral neuropathy (defined here as an abnormal neurological examination plus either abnormal nerve conduction or abnormal autonomic nerve testing) in insulin-dependent diabetes mellitus was shown with optimal glycaemic control. The problem has been determining how exactly hyperglycaemia translates into nerve injury, and thus how to prevent or treat this injury. In recent years there has been interest in the role of advanced glycation end products and the receptor for these (RAGE) and it seems likely that engagement of this receptor induces a spiral of cell dysfunction (Bierhaus et al, 2005) which might involve the peripheral nerve axon and myelin.

Oxidative stress is one reasonable downstream candidate for nerve damage, and there are several theoretical mechanisms why this might be generated: glucoxidation,

Figure 1. Causes of diabetic neuropathy.



mitochondrial dysfunction in sensory neurons and the polyol pathway particularly.

The polyol pathway generated significant therapeutic interest in recent years in terms of pharmacological interventions to prevent it. This pathway is activated when hyperglycaemia saturates the normal glycolytic pathway and extra glucose is shunted through other chemical reactions to form sorbitol and fructose, in the process using up NADPH and NAD+. The nerve membrane is relatively impermeable to sorbitol and fructose and these tend to accumulate, are osmotically active and increase the water content of the nerve. Accumulation of polyols is observed in animal models of diabetes mellitus and it was suggested that this could lead to neuropathy. In addition loss of NADPH starves glutathione reductase of its substrate, preventing the formation of reduced glutathione, which is necessary for the inactivation of superoxide.

Exactly how, at a molecular level, oxidative stress generates nerve damage is likely to be complex, possibly impacting on gene expression and altered cell phenotype. However, comparison of animal models and human nerve do not fully support all aspects of this theory and the aldose-reductase inhibitors which block this pathway have disappointingly failed to improve diabetic peripheral neuropathy in humans.

Ischaemia is thought to occur via numerous mechanisms: microvascular disease, large vessel disease, increased endoneurial resistance to hyperglycaemic blood, impaired endogenous fibrinolysis (Hafer-Macko et al, 2007) and the effects of advanced glycosylation end products. Any or all of these have the potential to destabilize the myelin sheath and promote degeneration of the axon to induce neuropathy.

Inflammation or vasculitis has particularly been suggested to cause focal and multifocal lesions such as cranial and radicular neuropathies. Multifocal proximal lesions can also produce the fairly symmetrical proximal radiculoneuropathy previously known as 'diabetic amyotrophy' (Said et al, 2003). Rarely, a superimposed inflammatory neuropathy (chronic inflammatory demyelinating polyradiculoneuropathy; CIDP) may occur.

All these mechanisms potentially lead to loss and dysfunction of the nerve axon, with secondary dysfunction of the myelin sheath (axons exert control over myelination) and also to dysfunction of the Schwann cell.

Types of diabetic peripheral neuropathy

Since the precise pathophysiology of diabetic peripheral neuropathy remains to be determined, classification tends to be a clinical descriptive one, simply described by Professor PK Thomas in 1997 (Thomas, 1997, adapted in *Table 1*). Sensibly he proposed that acute hyperglycaemia-related neuropathy, a rapidly reversible sensory syndrome possibly associated with nerve hypoxia in the setting of acute hyperglycaemia, is distinct from the other more persistent neuropathies.

Table 1. Clinical classification of diabetic peripheral neuropathy

Diffuse	Distal sensorimotor
	Autonomic
	Painful small fibre
	Acute painful
	Hyperglycaemic (acute)
Focal	Cranial
	Radiculopathy or plexopathy: limb, truncal or proximal
	Entrapment
	Lumbosacral radiculoplexopathy ('amyotrophy')

adapted from Thomas (1997)

By far the commonest (more than 80%) diabetic peripheral neuropathy is the distal symmetrical sensorimotor neuropathy, described below. This often exists together with the other diffuse neuropathies, particularly painful small fibre and autonomic neuropathy. Acute painful neuropathy is a rarer sensory syndrome which seems to occur in males, in association with severe rapid weight loss and depression, with intolerable lower limb pain, which usually improves over months with insulin and meticulous diabetic control.

Concurrent with the diffuse processes may be focal and multifocal neuropathies. Diabetic amyotrophy is now known to be a lumbosacral radiculoplexopathy and is an acute or subacute syndrome of usually asymmetric proximal pain, numbness, weakness and atrophy. Other focal or multifocal processes include cranial nerve involvement, especially the oculomotor and trochlear nerves, less commonly the abducens, and these usually spontaneously recover over 2 or 3 months.

Pathological studies of oculomotor nerves performed many years ago demonstrated centrofascicular ischaemic lesions in the intracavernous portions (Dreyfus et al, 1957; Asbury et al, 1970) with sparing of superficial fibres, explaining the common pupillary sparing. These more focal processes tend to be rarer in the young diabetic, being more commonly seen in patients over 50 years of age with longstanding diabetes mellitus, and are often self-limited or relapsing in nature, seemingly with more of an 'inflammatory' flavour.

In addition, entrapment neuropathies such as carpal tunnel syndrome are more common, possibly partly as a result of other aspects of the metabolic syndrome particularly obesity. However, other entrapments less associated with weight, such as ulnar neuropathies at the elbow (an unusual example is shown in *Figure 2*), are also more common, presumably because the already damaged nerve is more susceptible to compression. Such entrapments can respond to conservative or surgical treatments.

Distal sensorimotor neuropathy

Distal sensorimotor neuropathy is usually symmetrical and progresses following a length-dependent pattern with prominent sensory but also motor and sometimes autonomic manifestations. There is a spectrum of patients in this group, some with prominent pain, others with prominent sensory loss and there is a significant complication rate of ulceration and arthropathy.

The process tends to slowly progress or stay fairly stable over years, usually developing after several years of type 1 diabetes mellitus. However, diabetic peripheral neuropathy can herald the onset of type 2 diabetes mellitus, particularly in neurological practise, where patients not known to have diabetes mellitus are referred with symptoms of sensory neuropathy. This may be because intermittent hyperglycaemia and insulin resistance sufficient to damage distal nerves have been present for some time. Other components of the 'metabolic syndrome', especially abnormal lipid profiles, have also been associated with the development of neuropathy (Smith et al, 2008).

Inaugural symptoms include numbness, burning, pins and needles or other paraesthesiae and lightening pains, usually worst at night initially and often with allodynia (the perception of a painless stimulus as painful, such as the bed sheets on the feet). Alternatively distal sensorimotor neuropathy can be asymptomatic, only detectable on clinical examination (and, uncommonly, only detectable on nerve conduction studies) or may be heralded by trophic changes, ulceration or Charcot joints (*Figure 3*).

Although all sensory modalities are often affected if the patient is carefully examined, sometimes the syndrome predominantly affects the small nerve fibres which transmit pain and temperature. A 'pseudosyringomyelic type' was reported two centuries ago by Vergely in France in 1893 (with dissociation between pain and light touch). Pain can be prominent with elevation of warm temperature thresholds clinically, resulting in painless burns. Without careful foot care and daily patient vigilance, numbness allows the undetected progression of neuropathic ulcers. There is often prominent autonomic dysfunction suggesting similar changes occur in the unmyelinated autonomic fibres. Pain can be very dominant in some patients, and the discoveries relating sodium channel mutations to pain perception (Cox et al, 2006) suggest that this variability in response might turn out to be genetically determined.

Because standard clinical neurophysiology (electromyography or nerve conduction studies; EMG/NCS) only analyses the function of large nerve fibres, this may be normal if the neuropathy is predominantly small fibre, and this may direct clinicians away from the correct diagnosis. It can sometimes be helpful to have formal thermal threshold studies assessed or a skin biopsy analysed where there is doubt (Løseth et al, 2008) although often a clinical diagnosis can be made.

The prognosis of this common form of diabetic peripheral neuropathy is that, once the changes have occurred, they are probably irreversible, usually slowly worsen (progression is less with strict control of diabetes mellitus) and at best may stabilize.

Figure 2. a. Axial T1-weighted magnetic resonance image of the elbow of a diabetic patient with severe superimposed ulnar neuropathy at the elbow. An anconeus epitrochlearis accessory muscle is shown, extending across the cubital fossa from the medial cortex of the olecranon to the medial epicondyle, impinging on the ulnar nerve, which (b) appears bright on axial T2-weighted fat saturated image indicating neural damage.

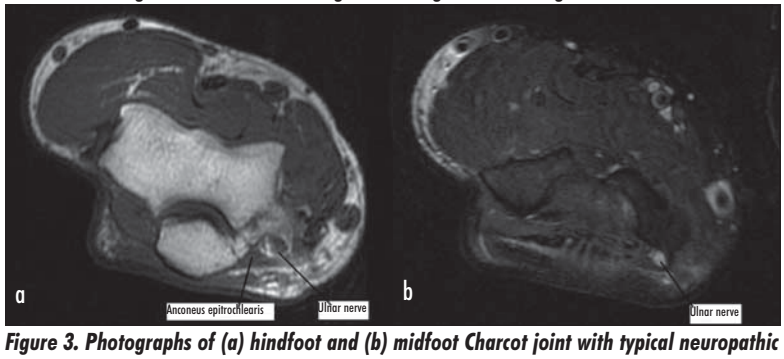
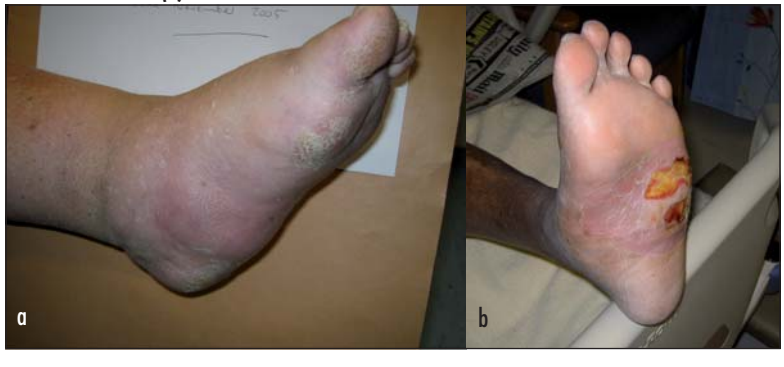


Figure 3. Photographs of (a) hindfoot and (b) midfoot Charcot joint with typical neuropathic ulceration seen in (b).



Investigation

When presented with a patient with suspected diabetic peripheral neuropathy, management starts with appropriate investigation. In a study of 100 diabetics with symptomatic neuropathy, in about three-quarters the diabetes mellitus was felt to be wholly responsible (Lozeron et al, 2002). In the others there were sometimes superimposed causes and certainly, particularly if atypical (e.g. rapid motor deterioration) it is appropriate to consider other causes such as inflammation (CIDP especially), alcohol, vitamin deficiencies, paraproteins, drugs and amyloid. If there is a very typical picture in a diabetic, EMG/NCS are not always necessary – and can be unhelpful early on if only the small fibres are affected, but EMG/NCS are very useful if the picture is atypical or focal. In a known diabetic patient, assessment of recent control using HbA_{1c} (glycosylated haemoglobin) levels is useful, and in patients presenting with length-dependent axonal neuropathy who are not known to have diabetes, fasting glucose and/or glucose tolerance testing is mandatory.

Treatment

Of distal sensorimotor neuropathy

Prevention of diabetic peripheral neuropathy must await effective treatment and prevention of diabetes mellitus, although fortunately there are other management strategies that can be extremely helpful.

The most logical treatment for established type 1 diabetes mellitus would seem to be the restoration of a long-lasting euglycaemic state. Although the first combined kidney and pancreas transplant was in 1967, the only really comprehensive study of the effects on diabetic peripheral neuropathy was 30 years later (Navarro et al, 1997) in a 10-year follow-up study which showed that, compared with diabetic controls in whom neuropathy worsened, those who had a transplant stabilized clinically and nerve conduction studies improved. Small fibre repair has been detected in the cornea using corneal confocal microscopy within 6 months of transplantation (Mehra et al, 2007). There is a long way to go before transplants for diabetes become routinely available and the majority of patients are managed by aiming for the best diabetic control possible. Ideally this (and transplantation) could be preventative for neuropathy rather than aiming to reverse it.

Patients with severe length-dependent sensory neuropathy are ideally managed in a multidisciplinary setting with access to diabetology, orthopaedics, vascular surgery, neurology, podiatry, orthotics and good nursing. The author is fortunate to have such a clinic and thus neuropathic pain and complications such as painless ulceration, Charcot joints (*Figure 3*), osteomyelitis and ischaemia can be diagnosed and treated rapidly. Access to excellent podiatry and advice regarding footwear should be mandatory. Even with such access, patients continue to present with acute deforming neuroarthropathy, requiring treatment in the author's experience with up to 6 months of non-weight-bearing measures (see below).

Numerous other treatments have been trialled and tried, aiming to interrupt the pathological processes by which hyperglycaemia causes neuropathy. The Cochrane Collaboration concluded that aldose reductase inhibitors have no effect on neurological function, that some have substantial side effects and that any future trials should be restricted to compounds with substantial biological advantage over those previously tested (Chalk et al, 2007).

Alpha lipoic acid (thioctic acid) is a potent antioxidant reported to improve neurophysiology and endoneurial blood flow in experimental animals and which also improves neuropathic symptoms if given either intravenously or orally (Ziegler et al, 2006). This drug is now licensed in several countries, although not in the UK. Benfotiamine, a lipid-soluble thiamine prodrug with high bioavailability, similarly is reported to have effects in animal models and, in a short pilot study, on human neuropathic pain. The Cochrane Collaboration have very recently reviewed the evidence for any vitamin B compounds in neuropathy and found this insufficient to enable a conclusion (Ang et al, 2008). Acetyl L-carnitine is deficient in diabetes and replacement in animal models is reported to correct disturbances of oxidation and free radicals with benefit on peripheral nerve function and structure. Benefit has also been shown for neuropathic pain in a subgroup of neuropathic diabetic patients for whom pain was the most important symptom (Sima, 2005).

In the UK these agents are mostly not part of the general care of a patient with diabetic peripheral neuropathy at present, although this may change if the evidence improves. In recent years, there has also been interest in using nerve growth factors to protect against experimental models of diabetic peripheral neuropathy and, again, these may have future therapeutic potential.

Of 'diabetic amyotrophy' – diabetic lumbosacral radiculoplexopathy

This condition often develops as diabetic control improves, especially in type 2 diabetes mellitus. No treatments have been shown to be of benefit to date. Slow recovery can occur but is not always complete.

Of autonomic neuropathy

Detailed discussion of the management of autonomic complications is outside the scope of this review. Orthostatic hypotension is fairly common, often exacerbated by antihypertensive medication, and if mild can be managed non-pharmacologically with compression stockings, careful standing with crossed legs and manoeuvres to increase the renin–angiotensin system such as raising the head of the bed at night. Medications such as fludrocortisone or midodrine are required if these measures are insufficient. Gastroparesis is also fairly common and can be difficult to manage, but can respond well to metaclopramide or domperidone, and by changing dietary habits with more frequent, small meals and reduced dietary fat and fibre.

Of neuropathic pain

Lists of medications used for neuropathic pain can be found in all medical textbooks, but most patients who describe unsatisfactory neuropathic pain control have tried very few appropriate treatments at sufficient dose. Of 151 patients with neuropathic pain, half of whom had diabetic peripheral neuropathy, 73% had inadequate control, even though opioids, tricyclic compounds and anticonvulsants had not been tried by 41%, 60% and 73% respectively (Gilron et al, 2002). These figures would concur with the author's experience that escalation of pain management is often inadequate in neuropathy.

In animal models neuropathic pain seems to be mediated by various mechanisms including alteration in the distribution of sodium channels, hyperexcitability of neurons and changes in spinal connectivity. Although

most treatments focus on one of these mechanisms, regardless of the underlying cause of painful neuropathy the therapeutic interventions are pretty much the same. In general, once an agent (*Table 2*) is selected, it is started at the lowest possible dose and slowly increased every 3–7 days until significant pain relief or intolerable side effects occur. If ineffective, the therapy should be stopped and another agent used. If all agents are ineffective, then combination therapy is needed (*Table 3*). Many treatment failures are the result of insufficient dosing or inappropriate dose escalation.

The mainstay of treatment are the antidepressants, particularly the tricyclics amitriptyline and imipramine (which is said to be less sedating) and the anticonvulsants, for which there is good evidence for efficacy. Amitriptyline, which blocks noradrenaline and serotonin release, has been shown to be beneficial independent of its effect on mood. The most important discussion to have with the patient is to make it clear that you are not using this because you think they are depressed, and to explain that this agent in low dose has been shown to have direct effects on the nerves. Pain relief does not usually occur until about a week after being on an appropriate dose and slow escalation (from 10 mg nocte in 10 mg weekly increments) to 75–150 mg has been required in most studies. Duloxetine was recently licensed in the UK for diabetic neuropathic pain following placebo-controlled trials but it has not been compared to tricyclics. The latest Cochrane review of antidepressants in neuropathic pain concluded that tricyclics are effective, that there was limited evidence for using the newer selective serotonin-reuptake inhibitors and no studies of serotonin and noradrenaline reuptake inhibitors and that venlafaxine was also found to be effective (Saarto and Wiffen, 2007).

Anticonvulsants are also very useful and again it is very important to start at low doses (*Table 2* and *3*). The author's experience suggests that starting doses should commence much lower than recommended in most drug formularies, although some (especially gabapentin) can be built up to high levels. Gabapentin remains very effective (Backonja et al, 1998) and pregabalin is a useful addition to the armoury (Lesser et al, 2004) and can be more effective in some patients. The main problem with the older agents is their drug interactions and side effects in patients who often have significant intercurrent illnesses and newer agents are thus increasingly used.

Opioids went out of favour for many years, but have now been shown to be useful for diabetic neuropathic pain, and controlled release oxycodone (10 mg CR twice daily initially, titrating up to a maximum of 60 mg/day) can be particularly useful (Gimbel et al, 2003).

Topical agents are reported to be especially useful for patients with painful burning feet. Capsaicin (0.075%) is an extract of chilli peppers which theoretically works by depleting substance P and other neuromediators in unmyelinated pain fibres, an attractive theory. It causes intense burning initially which generally wears off but is sufficiently uncomfortable for a high number of the author's patients to reject it. It may be that higher concentrations, administered as single applications with local anaesthesia, prove more useful. Topical local anaesthetics such as lidocaine, which now comes as a plaster, can also be useful for burning feet although they are not licensed for this.

Table 2. Neuropathic pain medications

Class	Agent	Initial dose
Antidepressants	Amitriptyline (tricyclic)	10 mg nocte
	Duloxetine (serotonin and noradrenaline re-uptake inhibitor)	30 mg once daily
Anticonvulsants	Gabapentin	300 mg once daily or 100 mg three times daily
	Pregabalin	75 mg once or twice daily
	Carbamezapine	100 mg once daily
	Sodium valproate	200 mg once daily
Topical	Capsaicin 0.075%	Three times daily
	Lidocaine gel patch 5%	For 12 hours every 12 hours
Opiates	Oxycodone (controlled release)	10 mg twice daily
	Tramadol	50 mg once daily

Table 3. Principles of chronic neuropathic pain management

Choose agent
Commence smallest available dose
Escalate dose weekly by same amount as original dose
Increase rate of escalation only if tolerated without any side effects
Continue slow escalation until reach therapeutic dose
Continue therapeutic dose in the long term
If agent ineffective, switch agent
If all agents ineffective, combine agents

Of other complications of diabetic peripheral neuropathy

Charcot joints

About 40 cases of acute Charcot neuroarthropathy have been managed in the author's clinic in recent years, and it is clear is that early diagnosis is very important. Initial signs of a hot swollen foot (often quite focally) are often confused with a ligamentous ankle injury or small metatarsal fracture, and if misdiagnosed the consequences can be dire. To prevent more inflammation and bony destruction, the foot requires complete off-loading of weight, ideally in a full-contact plaster of Paris cast, carefully changed every week or two with careful podiatric examination to detect and prevent neuropathic ulceration, and

with at least monthly clinical review. In this way the rate of consequent infection and infection can be made fortunately rare.

Neuropathic ulcers

Excellent chiropody and orthotics input, with careful detection and removal of callus, early detection and eradication of infection, and removal of pressure sources is essential. Prevention is obviously better than cure and impeccable foot hygiene and appropriate footwear with insoles and daily careful foot examination by the patient is most important.

Conclusions

It seems extraordinary that, in the 21st century, especially in medically-advanced societies, severe diabetic peripheral neuropathy and its devastating consequences are still so common. One would have hoped that the severely deformed neuropathic joint might be consigned to the historical texts, but sadly that is not the case. Prevention in established diabetes is not always possible, but optimal glycaemic control and fastidious attention to foot hygiene and footwear is really important. Drugs to treat diabetic peripheral neuropathy have not to date been particularly effective, but it is encouraging that treatment trials involve pathophysiologically feasible agents. It is hoped that these may be more effective if used in very early disease and that new interventional mechanisms will be discovered. Therapeutic neuropathic pain control is not just an aspiration, and should be possible for most patients. Things can only improve. **BJHM**

Figure 2 *is reproduced courtesy of Dr Elizabeth Dick, Consultant Radiologist, St Mary's Hospital, Imperial Healthcare NHS Trust and* Figure 3 *is reproduced courtesy of Dr Jon Valabhji, Multidisciplinary Diabetic Foot Clinic, St Mary's Hospital, Imperial Healthcare NHS Trust. Conflict of interest: Dr Gabriel has personally received sponsorship for meeting attendance from Pfizer.*

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KEY POINTS

- Up to 10% of diabetic patients have neuropathy at diagnosis.
- Up to 50% will have neuropathy after several years of diabetes.
- Hyperglycaemia is the cause of diabetic neuropathy, although the pathophysiology remains obscure.
- Although over 80% of diabetic neuropathy is distal sensorimotor axonal neuropathy, focal, ischaemic and inflammatory neuropathies also occur.
- Good podiatry is essential for the management of severe diabetic foot disease.
- The commonest cause of failure to treat neuropathic pain is inappropriate dosing.