Diabetic neuropathy: Review of diagnosis and management

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Diabetic neuropathy is common, under- or misdiagnosed, and causes not only substantial morbidity but also increased mortality. Apart from improving glycaemic control, there is no licensed treatment for diabetic neuropathy, although a number of pathogenetic pathways remain under active study. Focal and multifocal neuropathies are not common but can be extremely debilitating with few proven therapies. Autonomic dysfunction is more common, but significant deficits, although severe, are relatively rare, with limited therapeutic options. Painful diabetic neuropathy is a cause of considerable morbidity and many pharmacological as well as non-pharmacological interventions have been used. The recent NICE (2010) guidance provides an evidence-based rationale for the management of neuropathic pain in primary care.

Of all the long-term complications of diabetes, none affects so many organs or systems of the human body as the group of conditions termed the "diabetic neuropathies". Characterised by a progressive loss of nerve fibres, these conditions can be assessed by a variety of methods, varying from a structured neurological examination, through quantitative sensory testing, to detailed electrophysiology and autonomic function testing, as well as invasive procedures such as a nerve or skin biopsy (Boulton et al, 2004).

Whereas the rare symptomatic autonomic syndromes usually occur in people with long-duration type 1 diabetes, the mononeuropathies and proximal motor neuropathy usually occur in older people with type 2 diabetes (Boulton et al, 2004). The late sequelae of neuropathy are well recognised, with foot ulceration and Charcot's neuroarthropathy representing the most common cause of hospitalisation among people with diabetes in Western countries (Boulton et al, 2005).

In October 2009 a consensus panel of experts in diabetic neuropathy, which included leading diabetologists and neurologists, met in Toronto and agreed the following definition: "Diabetic neuropathy is a symmetrical length-dependent

Supported by a grant from MSD Diabetes. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. MSD had no input into the modules and is not responsible for their content.

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Learning objectives

After reading this article, the participant should be able to:

1. Describe the pathophysiology that underlies the different forms of diabetic neuropathy.
2. Discuss the epidemiology for the different forms of diabetic neuropathy.
3. Explain the main presentations and approaches to diagnosis of diabetic neuropathy.
4. Outline the investigations, treatment modalities and management options available for the differing diabetic neuropathies.

Key words
- Autonomic dysfunction
- Diabetic neuropathy
- Neuropathy
- Painful diabetic neuropathy

Author details can be found on page 171.

Page points

1. The quality and even quantity of epidemiological data on diabetic neuropathy remains poor for a number of reasons, including inconsistent definitions, poor ascertainment, lack of population-based studies, and failure to exclude non-diabetes-related neurological disease.
2. Distal sensory neuropathy is the most common of all the diabetic neuropathies, has a range of presentations and is often misdiagnosed, or not diagnosed at all, with extreme consequences such as foot ulceration.
3. In a recent analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial the presence of neuropathy was one of only three significant risk factors, including HbA_{1c} and aspirin use, that predicted mortality.
4. Autonomic neuropathy can manifest as cardiovascular, urogenital, gastrointestinal, thermoregulatory, and sudomotor dysfunction.

sensorimotor polyneuropathy attributable to metabolic and microvessel alterations attributable to chronic hyperglycaemia exposure and cardiovascular risk covariates" (Tesfaye S, personal communication). This is important as it acknowledges the role of cardiovascular risk factors in the development and progression of diabetic neuropathy (Tesfaye et al, 2005), and therefore offers the potential for intervention beyond improving glycaemic control, i.e. treating lipid levels and blood pressure.

The quality and even quantity of epidemiological data on diabetic neuropathy remains poor for a number of reasons, including inconsistent definitions, poor ascertainment, lack of population-based studies, and failure to exclude non-diabetes-related neurological disease.

Of three clinical-based studies in Europe (enrolling more than 2000 people), there was a remarkable similarity in prevalence, which varied from 22.5% to 28.5% for symptomatic neuropathy (Young et al, 1993; Tesfaye et al, 1996a; Cabezas-Cerrato, 1998). Similarly, in a community-based survey of 9710 people with diabetes derived from general practice in north-west England, the prevalence of moderate or severe neuropathic deficits was reported to be 22.4% (Abbott et al, 2002). However, these data are in contrast to a recent population-based study that used cluster sampling in Shanghai and reported a vibration perception threshold of ≥25 V in 59.1%, but an inability to feel the monofilament in only 13.8% (Lu et al, 2010).

Distal sensory neuropathy

Distal sensory neuropathy is the most common of all the diabetic neuropathies, has a range of presentations and is often misdiagnosed, or not diagnosed at all, with extreme consequences such as foot ulceration (Boulton et al, 2005). Thus, the person with diabetes may present with typical positive neuropathic symptoms such as burning pain; stabbing and shooting sensations; uncomfortable temperature sensations; paraesthesias, hyperaesthesias, and allodynia, yet the majority of individuals are not diagnosed correctly and are inappropriately treated (Hartsfield et al, 2008).

While symptoms fluctuate with time, when present, they tend to be extremely uncomfortable, distressing, and in particular are prone to nocturnal exacerbation with bedclothes hyperaesthesias. Alternatively, decreased pain sensation, deadness and numbness often require the practitioner to enquire about the lack of symptoms.

Controversy still exists as to which sensory modality is first affected, although small-fibre damage is already present even in people with impaired glucose tolerance (Boulton and Malik, 2010) and minimal diabetic neuropathy (Malik et al, 2005). Furthermore, in a recent analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial the presence of neuropathy was one of only three significant risk factors, including HbA_{1c} and aspirin use, that predicted mortality (Calles-Escandón et al, 2010).

Autonomic neuropathy

Autonomic neuropathy can manifest as cardiovascular, urogenital, gastrointestinal, thermoregulatory, and sudomotor (nerves that stimulate the sweat glands) dysfunction.

Cardiac autonomic neuropathy manifests initially as an increase in resting heart rate secondary to vagal denervation, followed by a decrease due to sympathetic denervation and, finally, a fixed heart rate that responds only minimally to physiological stimuli, bearing similarities to the transplanted and hence totally denervated heart. Again, in a recent analysis of the ACCORD data set the presence of cardiac autonomic neuropathy led to a 1.55–2.14 increased risk of death in the study participants (Pop-Busui et al, 2010).

A relatively rare but clinically significant manifestation is postural hypotension, defined as a 20 mmHg and 10 mmHg drop in the systolic and diastolic blood pressures, respectively, within 3 minutes of standing up from a lying position. This is thought to be due to sympathetic denervation and hence impaired vasoconstriction in the splanchnic and cutaneous vascular beds.

Autonomic neuropathy of the gastrointestinal tract presents with two major problems: diabetic

gastroparesis and erectile dysfunction (ED). The former is manifest by nausea and postprandial vomiting, and alternating nocturnal diarrhoea and constipation (Vinik et al, 2003).

ED is common but markedly underdiagnosed, as practitioners remain poor at enquiring about it, and people with the condition are not always forthcoming because it is perceived to be an embarrassing medical problem (Grant and Lipscomb, 2009). ED is usually of multifactorial aetiology and, although in most series autonomic neuropathy is a major contributory factor, consideration of other potential causes – including vascular disease, other medications, local problems such as Peyronie's disease, and psychological factors – is essential before a reflex prescription of the "blue pill".

Bladder dysfunction (cystopathy) is usually the result of neurogenic detrusor muscle abnormality and, in extreme cases, gross bladder distension may occur with abdominal distension and overflow incontinence.

Abnormalities of sweating are a common but often neglected symptom of diabetic autonomic neuropathy, most commonly presenting as reduced sweating in the feet due to sympathetic dysfunction. The Neuropad test has been shown to detect this abnormality at an early stage (Quattrini et al, 2008). Excess gustatory sweating – a profuse sweating over the head and neck on eating certain foods – is a highly characteristic symptom of diabetic autonomic neuropathy.

Focal and multifocal neuropathies

Focal and multifocal neuropathies are not unique to the person with diabetes and account for around 10% of all the neuropathies (Malik, 2002). Most tend to occur in older people with type 2 diabetes, and the prognosis is generally good with partial or complete recovery.

Exclusion of non-diabetic causes is particularly important in these neuropathies; in contrast, any person without diabetes with these presentations should be screened for the condition. Thus, in a series of 66 people with diabetes presenting with III, IV and VI nerve palsies, magnetic resonance imaging identified that 14% had a range of other pathologies, including skull-base neoplasms, brainstem infarcts, aneurysms, demyelinating disease and pituitary apoplexy (Chou et al, 2004).

The most common entrapment neuropathy is carpal tunnel syndrome (CTS), and significant independent determinants include a higher BMI, taking lipid-lowering medication and, interestingly, being in a stable relationship (Makepeace et al, 2008). There is a general perception that the severity of underlying nerve damage is more severe in diabetes-related compared with idiopathic CTS and that the results of surgical decompression are poorer. However, recent studies show comparable myelinated (Thomsen et al, 2009a) and intraepidermal nerve fibre (Thomsen et al, 2009b) loss with comparable clinical outcomes (Thomsen et al, 2009c) in people with CTS, with or without diabetes, undergoing decompression.

Other less frequent entrapment neuropathies include involvement of the ulnar nerve, lateral cutaneous nerve of the thigh (meralgia paraesthetica), radial nerve (wristdrop), and peroneal nerve (footdrop).

Truncal neuropathy is typically characterised by pain occurring in a dermatomal band-like distribution around the chest or abdomen and the differential diagnosis is shingles and spinal root compression.

Proximal motor neuropathy (also known as diabetic lumbosacral plexopathy and amyotrophy) typically affects older men with type 2 diabetes and characteristically presents with severe proximal pain, wasting and weakness. Based on the demonstration of mononuclear cell (CD4+, CD8+) and macrophage infiltration of epineurial and perineurial vessels in nerve biopsies (Dyck and Windebank, 2002), immunosuppression has been advocated, but a recent Cochrane review has shown that there are limited data to support this treatment (Chan et al, 2009). A demyelinating neuropathy suggestive of chronic inflammatory demyelinating polyneuropathy should be suspected in people with diabetes with a predominance of motor signs involving proximal or distal lower limb muscles – or if after some years of distal sensory neuropathy, a motor neuropathy develops with progressive symptoms and signs.

Page points

1. Erectile dysfunction is usually of multifactorial aetiology and, although in most series autonomic neuropathy is a major contributory factor, consideration of other potential causes – including vascular disease, other medications, local problems such as Peyronie's disease, and psychological factors – is essential before a reflex prescription of the "blue pill".
2. Excess gustatory sweating – a profuse sweating over the head and neck on eating certain foods – is a highly characteristic symptom of diabetic autonomic neuropathy.
3. The most common entrapment neuropathy is carpal tunnel syndrome, and significant independent determinants include a higher BMI, taking lipid-lowering medication and, interestingly, being in a stable relationship.
4. Proximal motor neuropathy (also known as diabetic lumbosacral plexopathy and amyotrophy) typically affects older men with type 2 diabetes and characteristically presents with severe proximal pain, wasting and weakness.

Page points

1. A totally inappropriate use of the 10-g monofilament is to '"diagnose neuropathy" as it will only detect advanced large-fibre neuropathy.
2. It is important to diagnose small-fibre damage as intervention must be aimed at a stage when there is a capacity for the nerve to repair, i.e. in the sub-clinical or mild neuropathy phase when small fibres are damaged.
3. It has been shown that corneal confocal microscopy – a novel non-invasive technique that scans the cornea – can detect small-fibre neuropathy in people with diabetes, comparable with intraepidermal nerve fibre density obtained from skin biopsies and can detect nerve repair after pancreas transplantation.

Diagnosis of neuropathy

Several different approaches have been used to diagnose and evaluate the severity of neuropathic deficits in diabetic neuropathy. The neuropathy disability score and 10-g monofilament have been recommended as screening tools in general practice to detect those at risk of foot ulceration (Abbott et al, 2002). However, data to suggest that the 10-g monofilament may not be reliable (Booth and Young, 2000) or optimal for identifying those at risk of foot ulcers (Miranda-Palma et al, 2005), have largely been ignored.

A totally inappropriate use of the 10-g monofilament is to '"diagnose neuropathy" as it will only detect advanced large-fibre neuropathy. Hence, a "normal test" may falsely reassure practitioners and people with diabetes, when in fact the individual may have mild neuropathy or indeed involvement of the small fibres. Therefore, the monofilament should only be used to detect those at risk of foot ulceration and not as a test for neuropathy.

A recent study by Perkins et al (2010) has shown that a score of ≤5/8 responses provides a high sensitivity (72%) and negative predictive value (87%) but a lower specificity (65%) and positive predictive value (46%), indicating that the monofilament could be used as an effective screening test to exclude the risk of developing neuropathy over approximately 4 years.

It is important to diagnose small-fibre damage as intervention must be aimed at a stage when there is a capacity for the nerve to repair, i.e. in the sub-clinical or mild neuropathy phase when small fibres are damaged (Malik et al, 2005). Quantitative sensory tests, including thermal threshold assessment for cold sensation (A-delta fibres) and warm sensation (C fibres), assess small fibre dysfunction, but are subjective with relatively low reproducibility (Mojaddidi et al, 2005).

People with diabetes with minimal neuropathy (normal electrophysiology and quantitative sensory tests) show significant unmyelinated fibre (Malik et al, 2005) and intraepidermal nerve fibre (IENF) damage (Quattrini et al, 2007; Umapathi et al, 2007; Løseth et al, 2008). Direct examination of these fibres can be undertaken via sural nerve biopsy with electron microscopy (Malik et al, 2001; 2005), and skin-punch biopsy (Sumner et al, 2003; Smith et al, 2005), however both are invasive procedures.

It has been shown that corneal confocal microscopy – a novel non-invasive technique that scans the cornea – can detect small-fibre neuropathy in people with diabetes (Hossain et al, 2005; Quattrini et al, 2007), comparable with IENF density obtained from skin biopsies (Quattrini et al, 2007) and can detect nerve repair after pancreas transplantation (Boucek et al, 2005; Mehra et al, 2007).

Treatment

Pathogenetic treatments

The ideal therapy should prevent or arrest the progressive loss of nerve function and repair nerves by interfering with the pathways that cause nerve damage. However, current

Table 1. Pathogenetic treatment options for diabetic neuropathy.

Mechanism of effect	Treatment	Drug	Dose per day (mg)	Side-effects	Comment
Glycaemic control	Insulin	–	–	Hypoglycaemia	Proven in type 1 but not type 2 diabetes
Glycaemic control	Pancreas transplantation[1]	–	–	Immunosuppression	Data limited
Oxidative stress	Alpha-lipoic acid[2]	Alpha-lipoic acid	600 mg IV 1200–1800 mg orally	–	No long-term data
Aldose reductase inhibition	Aldose reductase inhibitors[3]	Epalrestat	–	–	Only licensed in Japan
Improved blood flow	ACE inhibitors[4,5]	Trandolapril Lisinopril	2 mg 20 mg	Cough	More studies needed

[1]Mehra et al (2007); [2]Ziegler et al (2004); [3]Oates (2008); [4]Reja et al (1995); [5]Malik et al (1998). ACE=Angiotensin-converting enzyme; IV=Intravenous.

Table 2. Symptomatic treatment options for painful diabetic neuropathy.

Mechanism of effect	Class of drug	Drug	Dose per day (mg)	Side-effects	Comment
Pharmacotherapy	Tricyclic antidepressants	Amitriptyline[1]	20–150	+++	Sedation and anticholinergic side-effects.
		Imipramine[2]	25–150	+++	Sedation and anticholinergic side-effects.
	SNRI	Duloxetine[3]	60–120	++	Metabolic side-effects.
	Anticonvulsants	Gabapentin[4]	900–3600	+	Somnolence.
		Lamotrigine[4]	200–400	+	Nausea, headache.
		Carbamazepine[4]	200–600	++	Agranulocytosis.
		Pregabalin[5]	300–600	++	Pedal oedema, weight gain.
	Antiarrhythmics	Mexiletine[6]	Up to 900	+++	Nausea, tremor, increased arrhythmia risk.
	Opioids	Tramadol[7]	50–400	++	Sedation, constipation.
		Oxycodone[8]	40–60	+++	Sedation, constipation.
	Topical agents	Capsaicin[9]	Topical	+++	Intraepidermal nerve fibre loss.
		Gliceryl trinitrate[10]	Topical spray	++	Headache, tolerance.

[1]Max et al (1992); [2]Sindrup et al (2003); [3]Raskin et al (2006); [4]Wiffen et al (2005); [5]Freeman et al (2008); [6]Carroll et al (2008); [7]Freeman et al (2007); [8]Zin et al (2009); [9]Tandan et al (1992); [10]Agrawal et al (2009). +=Minimal; ++=Moderate; +++=Severe. SNRI=Serotonin–noradrenaline reuptake inhibitor.

treatment options only partially address the underlying cause of nerve damage (*Table 1*).

The DCCT (Diabetes Control and Complications Trial) and EDIC (Epidemiology of Diabetes Interventions and Complications) studies in type 1 diabetes (Albers et al, 2010) demonstrated not only prevention of progression with improved glycaemic control but also a "legacy effect" of early and effective glycaemic control on later progression of neuropathy. The UKPDS (UK Prospective Diabetes Study) in type 2 diabetes (Holman et al, 2008) also demonstrated a reduction in microvascular risk with early and effective glycaemic control, however it did not give specific data regarding prevention of progression of diabetic neuropathy.

Early and effective intervention is even more important with the recognition that neuropathy is present even in people with impaired glucose tolerance (Boulton and Malik, 2010). Additionally, increased blood glucose flux may contribute to painful diabetic neuropathy (Oyibo et al, 2002), which presents the case for the use of continuous subcutaneous insulin infusion in these individuals.

Interestingly, given the importance of vascular risk factors in the genesis of diabetic neuropathy (Tesfaye et al, 2005), there are two small studies that have shown an improvement in electrophysiology following treatment with angiotensin-converting enzyme inhibitors (Reja et al, 1995; Malik et al, 1998).

Recent data highlight the main challenge with future clinical trials assessing improvement in diabetic neuropathy, which is the lack of significant worsening of neuropathy in the placebo group (Dyck et al, 2007). This may reflect improved glycaemic control and, more probably, cardiovascular risk factors in people with diabetes as a result of the National Service Framework for diabetes (Department of Health, 2003) and the Quality and Outcomes Framework (Alshamsan et al, 2010).

Painful diabetic neuropathy

Peripheral damage of the small myelinated (A-delta) and unmyelinated (C) fibres is an essential prerequisite for the development of painful diabetic neuropathy. However, additional alterations that include both peripheral and central sensitisation make the treatment of this condition difficult. Hence, while many approaches have been advocated for the treatment of painful diabetic neuropathy, achieving >50% relief is rare and side-effects limit dose titration.

While the traditional approach has been to change or substitute treatments due to lack of efficacy or side-effects, a building body of data

Page points

1. While pharmacotherapy is the mainstay of therapy for the relief of painful diabetic neuropathy, alternative non-pharmacological treatments – such as acupuncture, transcutaneous electrical nerve stimulation, spinal cord stimulation, percutaneous electrical nerve stimulation, low intensity laser therapy and monochromatic infrared light – are used in people who are unresponsive or cannot tolerate pharmacotherapy.
2. Treatment of erectile dysfunction (ED) is primarily based on phosphodiesterase type 5 inhibitors, including sildenafil, tadalafil and vardenafil.
3. For those with ED who do not respond, intracavernous injections, intraurethral alprostadil, vacuum constriction devices or implantation of a penile prosthesis represent less attractive options.

suggests that combining lower doses of agents that act on different pain pathways may achieve better efficacy with fewer side-effects (Hanna et al, 2008; Baron et al, 2009; Zin et al, 2009). This establishes a new paradigm for future clinical trials in painful diabetic neuropathy (Backonja et al, 2006). The goal of this article is not to exhaustively detail all the studies in painful diabetic neuropathy as several recent excellent reviews and analyses provide this (Wiffen et al, 2005; Ziegler, 2008a; 2008b; Moore et al, 2009; Noble et al, 2010).

Table 2 provides a summary of available treatments, and the publication of the NICE guidance for neuropathic pain in March 2010 now provides a clear pathway on the treatment options for painful diabetic neuropathy in primary care (NICE, 2010).

While pharmacotherapy is the mainstay of therapy for the relief of painful diabetic neuropathy (Max et al, 1992), alternative non-pharmacological treatments – such as acupuncture (Abuaisha et al, 1998), transcutaneous electrical nerve stimulation (Kumar and Marshall, 1997), spinal cord stimulation (Tesfaye et al, 1996b), percutaneous electrical nerve stimulation (Hamza et al, 2000), low intensity laser therapy (Zinman et al, 2004) and monochromatic infrared light (Leonard et al, 2004) – are used in people who are unresponsive or cannot tolerate pharmacotherapy (*Table 3*); however, the evidence for these approaches is limited and needs to be carefully reviewed.

Table 3. Non-pharmacological symptomatic treatment options.

Mechanism of effect	Type of treatment	Comment
Physical therapy	Electrical spinal cord stimulation[1]	Highly invasive, limited data
	Transcutaneous electrical nerve stimulation[2]	Limited data
	Percutaneous electrical nerve stimulation[3]	Limited data
	Magnetic field therapy[4]	Limited data
	Low-intensity laser therapy[5]	Limited data
	Monochromatic near-infrared treatment[6]	Limited data
	Dressings[7]	Limited data
	Acupuncture[8]	Limited data
	Yoga[9]	Limited data
Others	Psychological support[10]	Limited data

[1]Daousi et al (2005); [2]Dubinsky and Miyasaki (2010); [3]Hamza et al (2000); [4]André-Obadia et al (2008); [5]Zinman et al (2004); [6]Harkless et al (2006); [7]Foster et al (1994); [8]Zhang et al (2010); [9]Malhotra et al (2002); [10]Yalcin et al (2008).

Autonomic neuropathy

Erectile dysfunction (ED)

Diabetes and cardiovascular disease are common risk factors for ED. Diagnosis is based on medical and sexual history, including validated questionnaires. An updated version of 2009 European Association of Urology guidelines on ED has been published recently (Eardley et al, 2010; Hatzimouratidis et al, 2010). Treatment of ED is primarily based on phosphodiesterase type 5 inhibitors, including sildenafil, tadalafil and vardenafil. For those who do not respond, intracavernous injections, intraurethral alprostadil, vacuum constriction devices or implantation of a penile prosthesis represent less attractive options.

Other autonomic neuropathies

Topical glycopyrrolate application appears to be effective and safe for the treatment of excessive facial sweating in gustatory hyperhidrosis (Kim et al, 2008). It is an antimuscarinic compound that, when applied topically to the affected area, results in a marked reduction of sweating while eating "trigger" foods, and its efficacy has been confirmed in a randomised controlled trial (Shaw et al, 1997).

Treatment of diabetic gastroparesis involves enhancing gastric motility and emptying. Metoclopramide, a dopamine antagonist, directly stimulates antral muscle and may also mediate acetylcholine release. Alternative agents include domperidone, a peripheral dopamine D2 receptor antagonist, or erythromycin, which directly stimulates motilin receptors (Ma et al, 2009).

Gastric neurostimulation has also been shown to be effective in people with gastroparesis refractory to medical therapy, the most difficult patients, although the evidence is limited to one randomised clinical trial and multiple non-randomised unblinded clinical trials and case series (Gonzalez and Velanovich, 2010).

Postural hypotension may be treated with mineralocorticoids such as fludrocortisone,

sympathomimetic agents and dopamine blockers (Low and Singer, 2008).

Urinary bladder difficulties are addressed with regular voiding, self-catheterisation and cholinergic agonists such as bethanechol chloride, which stimulates muscarinic, postganglionic receptors, enhancing bladder motility and emptying (Daneshgari et al, 2009).

Implications for primary care

Assessing those with painful diabetic neuropathy is not difficult, but it is often misdiagnosed and under or inappropriately treated. The new NICE (2010) guidance provides a comprehensive means to initially assess and treat individuals with painful neuropathy, together with timely referral to specialist care. More difficult manifestations of neuropathy, particularly autonomic neuropathy and foot ulceration, require early recognition and referral to specialist care. *Box 1* gives a case study highlighting some common problems encountered in primary care.

Conclusion

Diabetic neuropathy is a common complication of diabetes and can affect at least 50% of people with the condition, causing painful symptoms in approximately 20%. It is generally under- or misdiagnosed, causing substantial disability, and has also been shown to independently predict increased mortality.

There is no licensed treatment for diabetic neuropathy, but increasing evidence suggests that, in addition to poor glycaemic control, conventional cardiovascular risk factors may contribute to the development of the condition.

The focal and multifocal neuropathies are less common, but again remain underdiagnosed, especially median and ulnar neuropathies. Autonomic neuropathy has many manifestations that can have a significant effect on quality of life, especially for those with severe postural hypotension, diabetic gastroparesis and diabetic diarrhoea, for which there are limited treatment options. Painful diabetic neuropathy is also generally under- or misdiagnosed and inappropriately managed. NICE (2010) guidance provides an evidence-based rationale for the management of this condition. ■

Box 1. Case study.

Narrative

Mr B, a 57-year-old man with type 2 diabetes (diagnosed 9 years ago), presented to his GP with an HbA_{1c} level of 9.5% (80 mmol/mol). With the addition of gliclazide to his current regimen, this was significantly improved over the following 12 weeks to 7.2% (55 mmol/mol). Mr B then reported the development of burning and hypersensitivity to anything that touched his ankles or feet, with nocturnal exacerbation.

His treatment included metformin 1 g and gliclazide 160 mg twice daily, and simvastatin 40 mg, lisinopril 20 mg and aspirin 75 mg once daily. His blood pressure was 138/78 mmHg, his estimated glomerular filtration rate was 68 mL/min/1.73 m^2, and his total cholesterol level was 4.8 mmol/L. The 10-g monofilament exam was normal, as was vibration perception threshold. What is the diagnosis?

Discussion

This could be insulin neuritis, in view of the development of painful symptoms with rapid improvement in glycaemic control.

1. What would you do with regard to glycaemic control?
   – If this is insulin neuritis, then you should actually allow the HbA_{1c} level to rise to approximately 8% (64 mmol/mol).
2. Would you change the statin as his total cholesterol level is >4 mmol/L? There is limited evidence that improving lipids may improve neuropathy; in fact, the FIELD study showed a possible benefit with fenofibrate for reducing minor amputations (Rajamani et al, 2009). But remember, statins can also cause neuropathy.
3. How would you manage the painful neuropathy?
   – You should try to reduce overall glucose fluctuations. NICE (2010) recommends duloxetine, and if this is not tolerated or is ineffective either a tricyclic antidepressant or pregabalin, or a combination of duloxetine with pregabalin.

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"There is no licensed treatment for diabetic neuropathy, but increasing evidence suggests that, in addition to poor glycaemic control, conventional cardiovascular risk factors may contribute to the development of the condition."

CPD module

Online CPD activity

Visit www.diabetesandprimarycare.co.uk/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learned in practice.

1. **Which of the following risk factors is not associated with diabetic neuropathy? Select ONE option only.**
   A. HbA_{1c} level.
   B. Blood pressure.
   C. Body mass index.
   D. Triglycerides.
   E. Vitamin B12 levels.

2. **Painful diabetic neuropathy is associated with damage to which of the following? Select ONE option only.**
   A. Internal capsule
   B. Dorsal columns.
   C. A-alpha fibres.
   D. A-beta fibres.
   E. A-delta and C fibres.

3. **Which of the following statements correctly relates to the function, structure or assessment of small fibres? Select ONE option only.**
   A. They mediate light touch.
   B. Can be assessed using monofilaments.
   C. Can be assessed using electrophysiology.
   D. Can be assessed using corneal confocal microscopy.
   E. Have a myelin sheath.

4. **Which of the following treatments is recommended as the first-line management option for diabetic peripheral neuropathic pain in the recent NICE (2010) CG96 guideline for the management of neuropathic pain? Select ONE option only.**
   A. Amitriptyline.
   B. Morphine.
   C. Duloxetine.
   D. Gabapentin.
   E. Lignocaine patch.

5. **Which of the following statements correctly relates to painful diabetic neuropathy? Select ONE option only.**
   A. It is exacerbated by walking.
   B. It is associated with a raised erythrocyte sedimentation rate.
   C. It can be relieved with pregabalin.
   D. It can be relieved with lacosamide.
   E. It is not responsive to acupuncture.

6. **When considering autonomic neuropathy, which of the following symptoms is not a manifestation of the condition? Select ONE option only.**
   A. Diarrhoea.
   B. Vomiting.
   C. Bradycardia.
   D. Sweating.
   E. Erectile dysfunction.

7. **A 64-year-old man with type 2 diabetes (duration 14 years) and poor glycaemic control (HbA_{1c} level 9.7% [83 mmol/mol]) presents with pain and weakness in his right thigh. What is the diagnosis? Select ONE option only.**
   A. Diabetic painful neuropathy.
   B. Chronic inflammatory demyelinating polyneuropathy.
   C. Diabetic lumbosacral plexopathy.
   D. Insulin neuritis.
   E. Vitamin D deficiency.

8. **Mr W, aged 62, has had type 2 diabetes for a number of years. He thinks his control has been "not too bad". His wife died 5 years ago and he has just started a new relationship. He suggests that his sex life is failing and suspects it is due to his age. What action do you take? Select ONE option only.**
   A. Confirm that is likely to be the case.
   B. Tell him that the cause is likely to be psychological due to his long abstinence from sexual intercourse.
   C. He's heard people with diabetes can have Viagra (sildenafil) – you arrange a prescription.
   D. You refer him to the genitourinary clinic for specialist assessment.
   E. You consider his HbA_{1c} level, blood glucose monitoring results, blood pressure and general health and agree further consultations and tests.

9. **Mrs K, a 65-year-old woman with insulin-treated type 2 diabetes, presents to your surgery. She reports of early satiety, abdominal bloating and occasional vomiting after meals. Review of her blood glucose monitoring recordings show erratic readings. What is the likely diagnosis and likely first step in managing the problem? Select ONE option only.**
   A. Oesophageal neoplasm – arrange an oesophagogastroduodenoscopy.
   B. Gastroparesis – start metoclopramide therapy.
   C. Hiatus hernia – start proton pump inhibitor therapy.
   D. Gastroparesis – start domperidone therapy.
   E. Arrange a barium swallow – start domperidone therapy.

10. **A 59-year-old man has had poorly controlled type 2 diabetes for 12 years. During that time his HbA_{1c} level has not been less than 10% (86 mmol/mol). He is currently treated with insulin and metformin. He presents at your surgery with moderately severe pain in both buttocks and upper thighs. On examination, muscle wasting is noted around both upper thighs as well weakness on muscle extension. What is the most likely diagnosis? Select ONE option only.**
    A. Polymyalgia rheumatica.
    B. Multiple sclerosis.
    C. Proximal motor neuropathy (amyotrophy).
    D. An entrapment neuropathy.
    E. Lumbar disc prolapse.