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Diagnosing and managing diabetic somatic and autonomic neuropathy

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Abstract: The diagnosis and management of diabetic neuropathy can be a major challenge. Late diagnosis contributes to significant morbidity in the form of painful diabetic neuropathy, foot ulceration, amputation, and increased mortality. Both hyperglycaemia and cardiovascular risk factors are implicated in the development of somatic and autonomic neuropathy and an improvement in these risk factors can reduce their rate of development and progression. There are currently no US Food and Drug Administration (FDA)-approved disease-modifying treatments for either somatic or autonomic neuropathy, as a consequence of multiple failed phase III clinical trials. While this may be partly attributed to premature translation, there are major shortcomings in trial design and outcome measures. There are a limited number of partially effective FDA-approved treatments for the symptomatic relief of painful diabetic neuropathy and autonomic neuropathy.

Keywords: diabetic neuropathy, autonomic neuropathy, diagnosis, treatment

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Introduction

Diabetic peripheral neuropathy (DPN) occurs as a consequence of damage to the sensory, autonomic and motor nerves and can present with diverse symptoms and deficits (Table 1). The commonest presentations are those of somatic and autonomic neuropathy, and early diagnosis of these subtypes is recommended.[1] Small-fibre neuropathy can develop in patients with impaired glucose tolerance (IGT),[2] particularly those who develop type 2 diabetes mellitus (T2DM)[3] and it is recommended that patients with peripheral neuropathy should be evaluated for glucose dysmetabolism. However, the methods currently advocated to diagnose DPN, for example, neurological exam, monofilament and vibration sensation, detect moderate-to-severe large-fibre neuropathy, missing early small-fibre neuropathy.[4] Other causes of neuropathy, including B12 deficiency, and inflammatory neuropathies must be actively sought, as they are potentially treatable.[5,6] It is generally held that motor problems arise late in diabetic neuropathy, however recent studies show reduced muscle strength, volume and altered gait in patients with IGT and T2DM.[7–9] Furthermore, acute-onset severe pain and swelling in a proximal muscle, should also alert the physician to the occurrence of diabetic muscle infarction.[10] There is a threefold to fivefold higher prevalence of cranial[11] and peripheral mononeuropathies in patients with diabetes. Carpal tunnel syndrome is the commonest mononeuropathy in patients with diabetes[12] due to increased microangiopathy and vascular endothelial growth factor expression.[13,14] While bracing and splinting relieve pain, carpal tunnel decompression surgery outcomes are excellent and associated with recovery of neurophysiological function in patients with diabetes.[15]

Disease-modifying therapies for DPN

Improved glycaemic control can prevent the progression of diabetic neuropathy in T1DM, but not in T2DM.[16] This surprising result may be attributed to

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Table 1. Presentations of diabetic neuropathy.

Diabetic sensorimotor polyneuropathy
Predominantly small-fibre neuropathy
Predominantly large-fibre neuropathy
Mixed small and large-fibre neuropathy (commonest)
Atypical neuropathy
Isolated cranial neuropathy (III, IV, VI, VII)
Mononeuropathy (ulnar, median, peroneal)
Radiculopathy
Lumbosacral radiculoplexus neuropathy (amyotrophy)
Cervical/thoracic radiculopathy
Motor neuropathy
Reduced muscle volume and strength
Muscle infarction

late and less effective lowering of glucose in patients with T2DM and established neuropathy, concomitant weight gain and hypoglycaemia, and the use of insensitive endpoints.[17,18] Most of the studies assessing the effect of improved glycaemic control on neuropathy in T2DM were neither powered nor designed to show a benefit on neuropathy.[16] Cardiovascular risk factors, especially hypertension and triglycerides have been shown to play an important role in the development of diabetic neuropathy.[19] The STENO-2 study showed the overwhelming benefit of multifactorial risk factor reduction on cardiovascular outcomes,[20] mortality,[21] retinopathy, nephropathy and autonomic neuropathy, but not somatic neuropathy, as vibration perception was the endpoint for assessing neuropathy.[22] Indeed, a recent Japanese study has shown that intensive multifactorial intervention which led to an almost normalization of glycosylated haemoglobin (HbA1c) with weight loss and a reduction in blood pressure showed a significant improvement in neurophysiology and small-nerve-fibre repair, assessed using corneal confocal microscopy,[23] echoing the results of a previous study.[24] Early diagnosis and intervention may also be the key, as lifestyle intervention in patients with prediabetes improved sudomotor function and intraepidermal nerve-fibre density.[25] Indeed, smaller studies which have utilized more rigorous endpoints have shown a significant benefit on neurophysiology after treatment with an angiotensin-converting enzyme (ACE) inhibitor[26] and on neurological deficits and neurophysiology after treatment with an ACE inhibitor and calcium-channel blocker.[27] Statins or fibrates can also prevent the development of DPN,[28,29] reduce diabetic foot infection,[30] lower-extremity amputation[31,32] and increase healing of foot ulcers.[33] A *post hoc* analysis of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study has shown that the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide reduced ulcer-related foot amputation.[34] There are compelling experimental data showing a direct benefit of GLP-1 agonists on neuropathy.[35–37] This would suggest that the GLP-1 agonists may have potential benefits in the treatment of diabetic neuropathy[35] and a randomized clinical trial with rigorous endpoints is required to show this. The lack of rigorous and sensitive endpoints,[4] recruitment of patients with a broad spectrum of neuropathy severity and short trial durations have contributed to the failure of clinical trials in DPN.[17] Accurate phenotyping to select and stratify patients using sensitive endpoints targeting small-fibre repair (corneal confocal microscopy, skin biopsy) may allow trials of shorter duration to show an initial therapeutic effect. This would provide pharmaceutical companies with a go–no–go signal to invest in larger and longer trials, to gain US Food and Drug Administration (FDA) approval of disease-modifying therapies for DPN.[18]

Painful diabetic neuropathy

Painful diabetic neuropathy (PDN), a manifestation of small-fibre damage[38–40] is characterized by burning pain and significantly impacts on the patient's quality of life,[41–43] due to associated depression, anxiety and sleep disturbance.[42] It can affect 14.0–65.3% of patients with diabetes,[41,44–49] and the broad prevalence rates are attributed to different populations, risk factors and diagnostic methods. Paradoxically, the prevalence of painful symptoms may be higher in south Asians, despite a lower overall prevalence of neuropathy[50] and small-fibre neuropathy.[51] Despite the availability of a number of questionnaires, for example, the Douleur Neuropathique 4 (DN4) questionnaire,[52] Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale[53] and Neuropathic Pain Questionnaire (NPQ),[54] a large proportion of patients with PDN remain undiagnosed,[55,56] and 'suffer in silence'.[57] The risk factors for painful diabetic neuropathy include older age, duration of diabetes, presence of diabetic peripheral neuropathy,[41,44–46,48] obesity,[41,45,56,58] smoking,[44,58] poor glycaemic control,[59,60] low high-density lipoprotein (HDL) cholesterol,[41] elevated low-density lipoprotein (LDL) cholesterol, triglycerides and creatinine, [47] and vitamin D deficiency.[61,62]

Treatment of PDN

There is no evidence that improvement in glycemic control improves PDN; indeed, the opposite is true, where rapid and large reductions in HbA1c may precipitate an acute painful neuropathy.[63] The treatment of PDN has relied on trying different moderately effective therapies until one works, with minimal side effects. However, improved genotyping[64,65] and clinical phenotyping[66] may allow targeted mechanism-based therapies. Identifying patients with an irritable nociceptor can reduce the number needed to treat (NNT) for oxcarbazepine to 3.9 compared with 6.9 in patients with the nonirritable nociceptor.[67] Similarly, identifying patients with altered rate-dependent depression (RDD), a marker of descending inhibitory pathway dysfunction, may focus on those who will respond optimally to selective norepinephrine-reuptake inhibitors, for example, duloxetine.[68]

Tricyclic antidepressants (TCAs) mediate analgesic efficacy by indirectly modifying the opioid system in the brain and *via* neuromodulation of serotonin and noradrenaline.[69–71] A systematic review of 17 studies involving amitriptyline in 1342 participants in PDN trials showed moderate efficacy and caution, as there was a high risk of bias due to the small participant numbers in each study.[72] Duloxetine and venlafaxine potentiate the descending inhibitory pathways,[73] and a Cochrane review of eight randomized controlled trials (RCTs) with 2728 participants showed that duloxetine 60 mg daily had an NNT of five.[74] Although gabapentin is not FDA approved for the treatment of PDN, a recent Cochrane review has shown efficacy of this medication in DPN and it is widely prescribed. However, somnolence and dizziness limit dose titration and most patients do not receive the doses (1200–3600 mg) that have been shown to be efficacious.[75] Pregabalin is FDA approved for PDN, based on a number of RCTs.[76–78] Mirogabalin has recently shown efficacy and good tolerability in a phase II and two phase III clinical trials in DPN.[79–81] Tramadol may also be used second line, but a Cochrane review found that the efficacy of tramadol was determined in small inadequate-sized studies, with a risk of bias.[82] Tapentadol extended release is only the third medication to be recommended by the FDA for PDN.[83–86] The COMBO-DN study showed comparable neuropathic pain outcomes between a combination of duloxetine 60 mg daily and pregabalin 300 mg daily, compared with high-dose monotherapy of either duloxetine 120 mg daily or pregabalin 600 mg daily.[87] Furthermore, in an exploratory *post hoc* analysis, high-dose monotherapy was more favourable in patients with severe pain, whereas combination therapy was more beneficial in patients with mild-to-moderate pain.[88] There are few head-to-head studies comparing different drugs, but in a double-blind RCT in patients with PDN, analgesic efficacy was comparable between amitriptyline, duloxetine and pregabalin.[89] We have recently shown that treatment with vitamin D improves the severity of neuropathic pain[90] and quality of life in patients with PDN.[91]

Table 2. Symptoms and deficits in diabetic autonomic neuropathy.

Cardiac autonomic neuropathy
Resting tachycardia and/or fixed HR
Nondipping of nocturnal systolic BP
Orthostatic hypotension
Exercise intolerance
Syncope and light headedness
Painless myocardial infarction
Arrhythmias
Sudomotor neuropathy
Anhidrosis
Gustatory sweating
Urogenital autonomic neuropathy
Bladder dysfunction
(1) Nocturnal frequency and urgency
(2) Urinary hesitancy, weak stream, dribbling and urinary incontinence
Sexual dysfunction
Male: erectile dysfunction, decreased libido and retrograde ejaculation
Female: decreased sexual desire and arousal, inadequate lubrication
Gastrointestinal autonomic neuropathy
Nausea/vomiting
Bloating with inability to eat a full meal
Increased variability in blood sugar and hypos
Nocturnal diarrhoea

BP, blood pressure; HR, heart rate.

Autonomic neuropathy

Autonomic neuropathy is characterized by a range of symptoms and signs, which can be debilitating in a minority of patients, especially females with T1DM (Table 2). Cardiac autonomic neuropathy (CAN) *per se* is the strongest risk factor for all-cause mortality in T1DM and was an independent risk factor for mortality in the ACCORD study of patients with T2DM.[92,93] Hence, screening for CAN is recommended at diagnosis in T2DM and after 5 years in

T1DM.[1] The diagnosis of CAN includes documentation of the symptoms and signs, although there is a weak correlation between symptoms and autonomic deficits.[94,95] Cardiovascular autonomic reflex testing (CARTs) includes heart rate response to deep breathing, standing and the Valsalva manoeuvre.[96]

Disease-modifying therapies for autonomic neuropathy

The DCCT showed that intensive glycaemic control in patients with T1DM reduced the development of CAN by 45%[97] and the STENO-2 trial showed that intensified multifactorial treatment in patients with type 2 diabetes reduced the risk of CAN progression by 68%.[98,99] A small early study found favourable effects of alpha-lipoic acid (ALA) on CAN,[100] but a more recent study of triple antioxidant therapy (allopurinol, ALA and nicotinamide) showed no benefit.[101] There are currently no FDA-approved disease-modifying treatments for CAN.

Orthostatic hypotension

Symptoms of orthostatic hypotension (OH) occur on standing and include light headedness, weakness, giddiness and syncope. OH is defined as a blood pressure fall on standing >20/10 mmHg (>30/15 mmHg in those with BP > 150/90 mmHg) without an increase in heart rate (<15 beats per minute).[102] Treatment of OH involves fluid and salt repletion and encouragement of physical activity and exercise to avoid deconditioning.[103,104] Fludrocortisone is used but is not FDA approved for OH, and there are concerns over supine hypertension, hypokalaemia, congestive cardiac failure and peripheral oedema.[105] Both midodrine and droxidopa are approved by the FDA for the treatment of symptomatic neurogenic OH.[106]

Gastroparesis

Gastroparesis may present with bloating, nausea and overt recurrent vomiting, necessitating admission to hospital, or may underlie unexplained variability in blood sugars. It is defined as the delayed removal of stomach contents in the absence of a physical obstruction.[107] Gastric emptying should be formally assessed at 15-min intervals, with scintigraphy 4 h after food intake of digestible solids. Metoclopramide is the only FDA-approved drug for the treatment of gastroparesis, but limited efficacy and the risk of tardive dyskinesia has led the FDA and European Medicines agency to limit its use to a maximum of 5 days. New therapies currently being investigated include motilin-receptor agonists, ghrelin-receptor agonists, and neurokinin-receptor antagonists. Mechanical options for intervention include transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy and in severe intractable gastroparesis, laparoscopic pyloroplasty or gastrectomy may be options.[108]

Diabetic diarrhoea

Diarrhoea occurs twice as frequently in diabetic patients and of course may be related to pancreatic exocrine insufficiency, bariatric surgery, and drugs such as metformin and GLP-1 agonists.[109,110] Pharmacological therapies include antibiotics to eradicate bacterial overgrowth, somatostatin analogues, and selective serotonin 5-hydroxy tryptamine type 3 (HT3) receptor antagonists.[111,112]

Bladder dysfunction

Bladder dysfunction may occur in 50% of patients with diabetes due to urogenital autonomic neuropathy.[113] Increased initiating threshold for the micturition reflex is followed by decreased detrusor activity and incomplete bladder emptying. The diagnosis should be based on urodynamic studies and the assessment of residual bladder volume. Treatment includes suprapubic pressure, intermittent self-catheterization, anticholinergic medication for detrusor hyperreflexia and parasympathomimetic medication to reduce detrusor contractility.[114]

Sudomotor dysfunction

A reduction or loss of distal sweating due to sympathetic denervation of the sweat glands is common[115,116] and can precipitate a break in the skin, leading to foot ulceration. It can be assessed using neuropad®[117–119] (Miro Verbandstoffe, Wiehl, Germany) or Sudoscan™[120] Impeto Medical, Paris, France to risk stratify patients with DPN.[121]

Erectile dysfunction

Erectile dysfunction (ED) in patients with diabetes is three times more prevalent, may occur 10–15 years earlier and is less responsive to treatment, compared to patients without diabetes.[122] ED is associated with a higher HbA1c, presence of metabolic syndrome, hypertension, dyslipidaemia,

lower estimated glomerular filtration rate, higher albumin/creatinine ratio and more severe small-fibre neuropathy.[123–125] Around 47% of women with diabetic neuropathy also have sexual dysfunction characterized by reduced sexual arousal, decreased lubrication and painful intercourse.[126] Recent recommendations include active smoking cessation (improves ED by ~30%), testosterone replacement in those with testosterone deficiency, statins, phosphodiesterase type 5 inhibitors, intracavernosal and transurethral prostaglandins, and penile implants for more severe cases.[127–129]

Diabetic somatic and autonomic neuropathy have a significant impact on morbidity and mortality in the diabetic patient and yet remain woefully underdiagnosed and inadequately managed. Although there are currently no FDA-approved disease-modifying therapies, there is evidence that improvement in vascular risk factors alongside glycaemia may have a beneficial effect. Moderate relief of symptomatic, painful and autonomic neuropathy is possible, but requires early recognition and tailored intervention.

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