

A review of diabetic peripheral neuropathy management given recent guidelines updates.

Ehab Hamed*, Mohalall Abdel Monem

Department of Family Medicine, Al Khor Health Centre, Primary Health Care Corporation, Qatar

Abstract

American Diabetes Association (ADA), Diabetes Canada (DC) published updates to the management of Diabetic peripheral neuropathy (DPN) in 2017 and 2018. National Institute of Healthcare and excellence (NICE) also updated their guidelines for management of neuropathic pain in 2018.

This article aims to review the topic given those updates and to highlight similarities as well as differences in management. The authors will focus on implications and their clinical application in everyday practice.

Keywords: Diabetes peripheral neuropathy, Neuropathic pain, Diabetes complications.

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Introduction and Background

Diabetic peripheral neuropathy (DPN) is common with prevalence ranging from 40% to 50% of all patients with long-standing diabetes [1]. DPN term refers to peripheral nerve dysfunction and damage in diabetic patients after exclusion of other causes [2]. The definition encompasses a heterogeneous group of presentations.

Clinical presentation of DPN could be asymptomatic, typical neuropathic pain, atypical neuropathic pain, altered or decreased sensations. Motor or sensorimotor symptoms may present early on in the form of weakness and wasting. Asymptomatic DPN is not uncommon. Typical neuropathic pain refers to the typical presentation of stocking and gloves pain. Atypical neuropathic pain covers many forms of peripheral neuropathic pain that varies in site and character. Pain could be refractory to treatment and affects patient quality of life. Lastly, sensory symptoms may present in the form of altered or decreased sensations. Both of which are a risk factor for diabetes complications such as diabetic foot, ulcers and amputations. Complications of DPN are significant causes of morbidity and mortality in the diabetic population [3].

The mainstay of treatment should remain on prevention rather than reversibility. To date, once DPN developed no treatment is available to reverse the condition or to alter the progression course. Tight Glycaemic control may be an effective intervention to prevent or delay the development of the condition in type 1 diabetes. It may help reduce the clinical neuropathy symptoms and signs in both types of diabetes [2,4,5]. The focus of treatment of DPN is currently on improving quality of life and preventing complications through effective screening, pain control and foot care.

Subclinical and clinical DPN and other classifications

Subclinical DPN refers to patients with no symptoms but definite signs and positive nerve conduction studies. Symptoms of DPN are absent in up to 50% of diabetic peripheral neuropathy patients [6]. Clinical DPN refers to patients with both symptoms and signs.

Classification of DPN according to nerve distribution includes polyneuropathy, mononeuropathy, mononeuropathy multiplex among other presentations. Also, peripheral nerve dysfunction could be sensory, motor or both if classified according to function.

Symptoms and signs

In clinic settings, symptoms and signs are both crucial for screening for and assessing the severity of DPN.

The most frequent presentation of DPN is the symmetrical sensory pain/impairment that affects lower limbs sooner than the upper limbs in a classic stocking and gloves' appearance [7]. Other symptoms to suggest DPN include atypical pain, altered sensation, numbness, pins and needles, hot or burning sensations. More interestingly, painful symptoms could happen in diabetic patients with or without neuropathy [8]. Neuropathic motor dysfunction symptoms include muscle weakness, poor balance and falls.

Signs of neuropathy tested at the bedside include vibration sensation and altered proprioception, which reflect large-fibre function. Also, impairment of pain, light touch, and temperature which reflects small fibres' functions, Any of which could present as an early sign of neuropathy [9]. Motor signs include wasting and decreased reflexes. Motor and sensorimotor neuropathy symptoms and signs are all reported and recognised complications of diabetes.

Both symptoms and signs carry subjective elements and could be nonspecific. 10 g Monofilament and tuning fork had low and variable diagnostic accuracies with the former sensitivity reported from 19% to 73% in one systematic review [10].

Several scoring systems are in place for identification of DPN cases. The United Kingdom screening test (UKST) [11] and the Michigan Neuropathy Screening Instrument (MNSI) [12] are among the commonly used tools. The 2 part diagnostic screening tools consist of simple symptoms and physical examination scores (Table 1).

Either could serve as a gold standard history taking and examination tools. Both screening tools have better specificity and sensitivity but are time-consuming. It is not clear though that these complex systems have beneficial outcomes compared to the simplified screening [1].

Nerve conduction study and a validated measure of small fibre neuropathy are the gold standards to establish the diagnosis of typical DPN and to monitor the severity. They are not readily available in the community and many clinic settings, but they could play an essential role in at least epidemiological and research purposes [13].

Generally, the diagnosis of DPN remains clinical diagnosis. More than one symptom or sign at presentation or combination of both are stronger predictors of diabetic neuropathy. Current guidance from ADA and DC does not support the usage of more scoring systems.

Frequency and mode of bedside assessment

In 2017 statement the American Diabetes Association (ADA) recommended that all type 2 patients should be assessed with history taking and bedside testing at the time of diagnosis and at least annually afterwards. Those with type 1 should be assessed five years after diagnosis and again annual testing. Diabetes Canada (DC) 2018 guidelines seem to agree with the frequency of check. Both reflect on the early presentation of DPN in type 2 patients.

On the mode of testing, The ADA recommends bedside testing with temp or pinprick sensation and tuning fork to test both small and large nerve fibre functions. 10 g monofilament testing is essential in all patients [2]. DC recommends rapid screening using either monofilament or tuning fork annually in asymptomatic patients (Table 2). More comprehensive

testing, including scoring systems, could be used for those with symptoms or positive signs and for research purposes [1].

Patient with prediabetes might benefit from baseline assessment at the time of diagnosis. A holistic evaluation of diabetic foot risk should include reviewing skin integrity, vascular systems, footwear and cardiovascular risk factors.

Investigations and differential diagnoses

History, examination alongside investigations could help exclude other causes of neuropathy. Symptoms and signs that would warrant referral include an asymmetrical presentation, rapid progression and motor more than sensory signs. In everyday practice, recommended blood tests include serum B12, folic acid, thyroid functions, complete blood count and serum electrophoresis [14].

Patients with diabetes are likely to have B12 and Thyroid-function abnormalities. B12 deficiency is more associated with malabsorption rather than nutritional deficiency [2]. Specifically, In type 2 diabetes population, B12 deficiency is more relevant because of long-term metformin use [15]. On the other hand, The thyroid stimulating hormone (TSH) was higher in a Chinese population with DPN, and in another systematic analysis, subclinical hypothyroidism was associated with more diabetic complications [16,17]. A periodic check of both B12 and TSH is a reasonable approach in all diabetic patients with or without neuropathy.

Prevention and tight glycemic control

Prevention approach focuses on glycemic control. In type 1 diabetes near-normal glycemic control reduces the occurrence of DPN, and patient with intensive treatment showed the benefits of primary prevention for more than ten years [18]. In

Table 1: The United Kingdom screening test (UKST) vs Michigan neuropathy screening instrument (MNSI).

	UKST	MNSI
Symptoms	(a) What is the sensation felt? (b) What is the location of symptoms? (c) Have the symptoms ever woken patient at night? (d) What is the timing of symptoms? (e) How are symptoms relieved?	1. Are your legs and/or feet numb? 2. Do you ever have any burning pain in your legs and/or feet? 3. Are your feet too sensitive to touch? 4. Do you get muscle cramps in your legs and/or feet? 5. Do you ever have any prickling feelings in your legs or feet? 6. Does it hurt when the bed covers touch your skin? 7. When you get into the tub or shower, are you able to tell the hot water from the cold water? 8. Have you ever had an open sore on your foot? 9. Has your doctor ever told you that you have diabetic neuropathy? 10. Do you feel weak all over most of the time? 11. Are your symptoms worse at night? 12. Do your legs hurt when you walk? 13. Are you able to sense your feet when you walk? 14. Is the skin on your feet so dry that it cracks open? 15. Have you ever had an amputation?
Signs	(a) What is the Achilles tendon reflex? (b) What is the vibration sense? (c) What is the pin-prick sensation? (d) What is the temperature sensation?	1. Appearance of Feet 2. Ulceration 3. Ankle Reflexes 4. Vibration perception at great toe 5. Monofilament

Table 2: Frequency and mode of assessment.

	ADA	DC
Asymptomatic patients mode of assessment	Temp or Pinprick +Tuning fork +monofilament	Either Monofilament or tuning fork
Symptomatic patients	More comprehensive testing	
Both Guidelines recommend annual testing of all type 2 patients from diagnosis and type 1 patients 5 years after diagnosis. Healthcare professionals should assess risk in at least three different sites on each foot.		

Table 3: Pain management medications in DPN.

	ADA	DC	NICE
	Pregabalin Gabapentin	Pregabalin Gabapentin Valproate	Pregabalin Gabapentin
	Duloxetine Venlafaxine	Duloxetine Venlafaxine	Duloxetine
	Nortriptyline Desipramine	Amitriptyline	Amitriptyline
		Topical nitrate sprays Topical capsaicin	Capsaicin cream
Notes	1. The choice should be patient specific 2. Starting dose should be low and titrate up according to the response. 3. In non-responders, healthcare professionals should switch between agents. DC guidance suggests they may also be used in combinations. 4. Tramadol and Tapentadol carry risks of tolerance, abuse and dependency. They may be considered in people not responsive to the above medications.		

type 2 tight control is reported as a modestly useful measure for prevention [1,2]. There is no evidence to date that tight glycemic control reverses DPN course, but it is paramount for managing patient cardiovascular risk and preventing complications.

Management of diabetic neuropathy pain

Painful diabetic neuropathy affects 25% to 30% of patients with diabetes in both hospital and clinic settings. Patients are reluctant to report their symptoms, and many of them do not take their medications. Few patients report complete relief of pain, and 30 to 50 % reduction is considered a meaningful response [19].

Medications fall into three categories, anticonvulsants, antidepressants and opioids. Antidepressants are further divided into serotonin-norepinephrine reuptake group and tri-cyclic antidepressants (TCA) group. All categories have their common share of side effects and significant adverse events. Anticonvulsants and antidepressants are more favourable options compared to opioids because of their less addictive profile.

American Diabetes Association (ADA) treatment guidance elected two medicines from each treatment group as possible first lines. It favours pregabalin and gabapentin as options from the anticonvulsants group, duloxetine and venlafaxine from the serotonin-norepinephrine reuptake inhibitor group and finally nortriptyline and desipramine from the tri-cyclic antidepressants group.

The guidelines allow physicians to choose according to patient comorbidities, side effects, drug interaction and cost. Of this list, FDA approved only pregabalin and duloxetine for the management of pain in diabetic neuropathy patients [2]. Canadian Guidelines affirms there is not enough evidence for comparative effectiveness. It also highlights the same two medicine as licensed medications in the treatment of the condition from Health Canada [1].

Pregabalin and duloxetine numbers needed to treat (NNT) range from 3.3 to 11 for 30 to 50% of pain reduction. TCA group have better numbers with NNT falls below three but more side effects. In other words, about two-thirds of patients may not respond to treatment, and most patients have a partial response. Other alternatives include topiramate, venlafaxine, amitriptyline, nortriptyline and desipramine and topical nitrate spray.

Options from the opioid family include tramadol and tapentadol with the latter gained the license for treatment of the condition. Both the ADA and Canadian Guidelines suggest that physicians should not use opioid agents as first lines of treatment because of their higher potential for abuse.

National Institute of Health and Care Excellence (NICE) suggested a choice of amitriptyline, duloxetine, gabapentin or pregabalin as the first line. They advise to switch in between those agents if the patient is not responding or developing side effects (Table 2).

NICE recommends referral to a pain specialist in case of treatment poor response or effect on patient quality of life. Tramadol is suggested for acute therapy and capsaicin cream for those patients who have localised pain and don't want oral medicine [20].

All current guidelines advise a personalised approach with a low dose start to be tailored to the maximum response with the least side effects or adverse events. Early rotation or switch to another agent in treatment failures, side effects or adverse events (Table 3). Painful diabetic neuropathy (PDN) can be refractory to conventional pharmacologic therapy [21].

Other options for pain management

Other options for pain management include surgical decompression and alternative and complementary medicine approaches.

Surgical decompression is an evolving field. A recent systematic review suggests it may be beneficial in DPN cases, though the evidence comes from observational studies and more focused towards upper limb presentations [22,23].

Alternative and complementary medicine approaches with promising results from the latest literature systematic reviews include alpha lipoic acid, acetyl-L-carnitine, spinal cord stimulation and capsacian [24-27]. Acupuncture and chinese medicines have less evidence to support its use.

Beyond pain management

NICE recommendations stress following a personalised approach with an agreed treatment plan that takes into account patient concerns, expectations and health beliefs. It stresses the importance of assessing the impact on life, explaining plans for

starting, titrating up doses and monitoring. It follows up on other coping strategies and rehabilitation programmes and referral to pain specialists when necessary [20].

Multifactorial care includes optimisation of cardiovascular risk factors such as lifestyle, dyslipidemia, HTN, erectile dysfunction and stress. It is also essential to assess the effect of pain on psychological status. It may improve patient responses and adherence to treatment. Diabetic peripheral neuropathy was associated with a higher risk of depression and anxiety [2].

Complications

Diabetic foot ulcers, infections, gangrenes and amputations are associated with higher mortality and poor prognosis. 50% of patients with amputations and foot ulcers die within five years [28]. The classic triad of ischemia, neuropathy and infection caused a casual sequence of trauma, ulcer, and infection in nearly 72% of amputation cases. While the primary pathology is diabetic vasculopathy, a five-year retrospective study reported neuropathy as the main etiopathogenetic factor for diabetic foot [29].

The term foot care encompasses a patient and physician approach to screen for neuropathy, vasculopathy and infection signs. Multidisciplinary team urgent intervention may be required in the event of ulceration and development of diabetic foot.

Conclusion

Diabetic peripheral neuropathy is a clinical diagnosis that is well researched with recent updates on management. Combination of symptoms and signs improves the accuracy of screening and diagnosis. Healthcare professionals should consider referral in cases with rapid progression, motor more than sensory and asymmetrical presentations. Current guidelines suggest routine blood investigations checks with a focus on vitamin B12, thyroid function tests and serum electrophoresis. Tight glycaemic control forms a cornerstone in the prevention or delay of presentation, and it may prevent complications.

Pain control should be patient centred, regularly monitored and tailored to minimum effective dose with least side effects. There is a consensus on the usage of pregabalin, gabapentin, duloxetine and to less extent venlafaxine and amitriptyline. In many cases, pain could be refractory to medicine.

A more holistic approach should address the impact of diabetic neuropathy on a patient's quality of life, psychological status and assessment of other cardiovascular risk factors. Screening, early detection and urgent intervention may help decrease diabetic foot complications and amputation rates.

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***Correspondence to:**

Ehab Hamed
 Department of Family Medicine
 Al Khor Health Centre
 Primary Health Care Corporation
 Qatar
 E-mail: eshamed@phcc.gov.qa