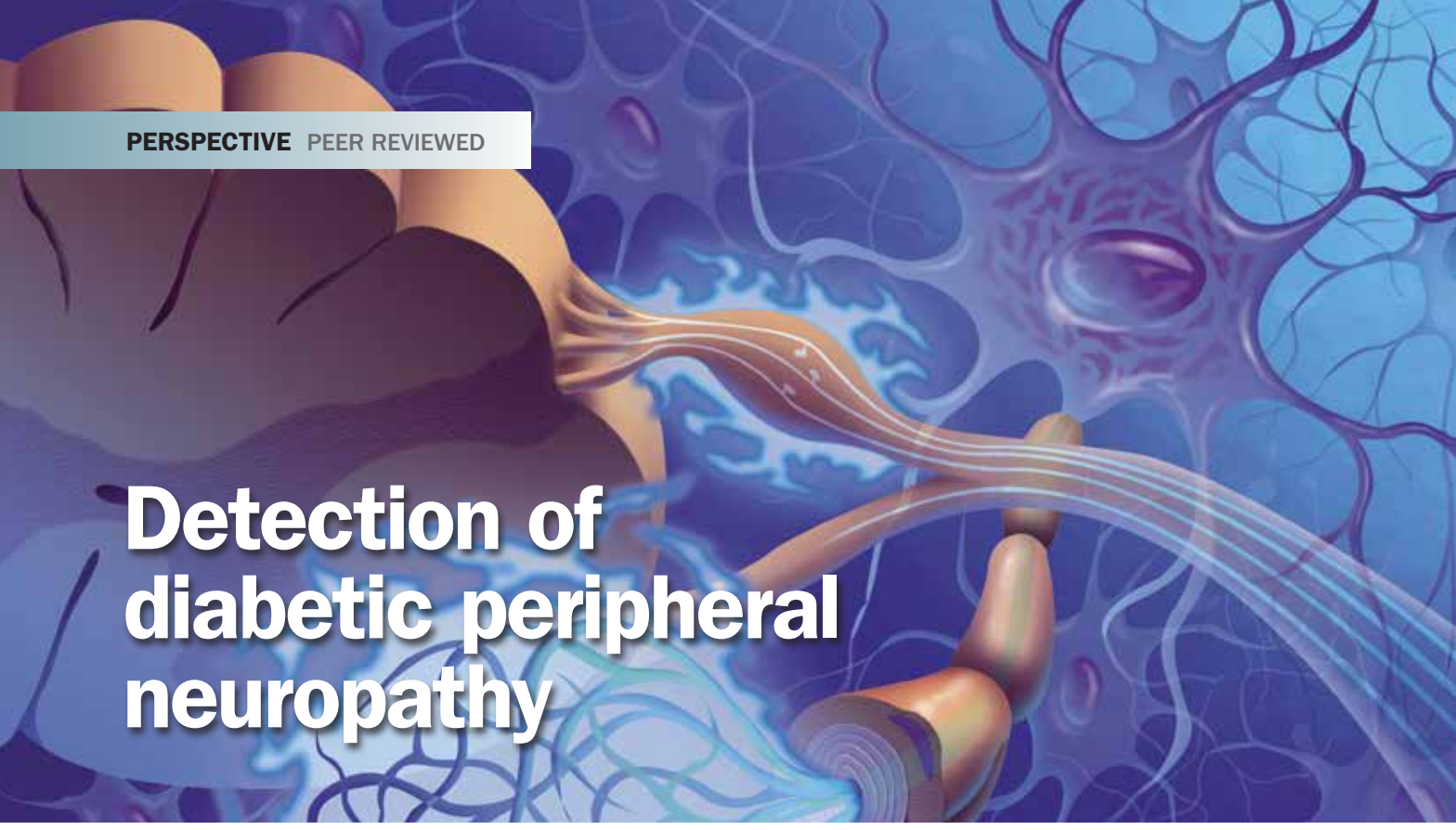

Detection of diabetic peripheral neuropathy

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Patients with diabetic peripheral neuropathy may have few symptoms but are at risk of developing foot ulcers and Charcot deformities. Early detection of diabetic neuropathy is therefore important to identify patients who would benefit from tighter glycaemic control and attention to contributing risk factors to help prevent the development of these complications.

Key points

- **Peripheral neuropathy may be present at diagnosis of prediabetes or type 2 diabetes.**
- **Peripheral neuropathy may be present without symptoms.**
- **Both symptomatic and asymptomatic peripheral neuropathy places the person at risk of ulceration.**
- **Patients with significant peripheral neuropathy benefit from podiatry review.**
- **An atypical presentation, such as asymmetry or prominent early motor signs, warrants nerve conduction studies and referral of the patient to a neurologist.**

ENDOCRINOLOGY TODAY 2015; 4(3): 21-24

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Diabetic peripheral neuropathy can be a painful, debilitating complication of type 1 and type 2 diabetes. The severity of nerve dysfunction correlates strongly with a patient's quality of life.[1] Patients with diabetic peripheral neuropathy may have few symptoms but are at risk of developing foot ulcers and Charcot deformities. Early detection of diabetic neuropathy is therefore important to help prevent the development of these complications and reduce the risk of amputation. Improvement in diabetes control can slow the progression of peripheral neuropathy in people with type 1 diabetes.[2] Patients with prediabetes and peripheral neuropathy have shown improvement in nerve function and reduction in painful symptoms with improved blood glucose levels.[3] Unfortunately, some studies have shown less effect on the development and progression of peripheral neuropathy with intensive treatment of type 2 diabetes,[4] probably reflecting the long prodrome of type 2 diabetes.

There are many forms of diabetic neuropathy including symmetrical polyneuropathy, autonomic neuropathy, mononeuropathies and mononeuropathy multiplex. This article focuses on symmetrical diabetic polyneuropathy.

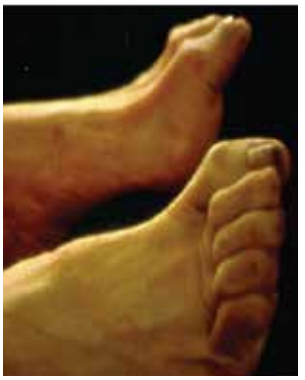

Figure 1. Clawed toes.

Figure 2. A callus overlying ulceration.

FIGURES COURTESY OF PROF TWIGG, Ms McCOSTER, Ms BOLTON, ROYAL PRINCE ALFRED HOSPITAL, SYDNEY, NSW.

Diabetic polyneuropathy

Diabetic polyneuropathy is a symmetrical primarily sensory polyneuropathy, which initially affects the distal lower limbs. Approximately 10% of patients have evidence of peripheral nerve damage at the time of diagnosis of type 2 diabetes and this increases to 40% after 10 years of having diabetes.[5] Patients with prediabetes can also present with peripheral neuropathy, suggesting that even mild dysfunction in glucose regulation can cause nerve damage. It had been thought that peripheral neuropathy does not develop until after five years' duration of type 1 diabetes, but newer techniques have revealed nerve excitability changes in patients with type 1 diabetes with normal nerve conduction.[6] Similarly, when people with type 2 diabetes were studied with techniques specific for small nerve fibre dysfunction or loss (quantitative sensory testing and/or epidermal nerve fibre density analysis on skin biopsy), those with small fibre sensory neuropathy but normal nerve conduction were identified.[7] As the disease progresses up the legs to the midcalf, sensory loss can appear in the hands, causing the typical 'glove and stocking' pattern. Motor involvement can occur in the same distribution, but usually occurs later on and in more severe cases.

Symptoms

The earliest signs and symptoms of diabetic polyneuropathy relate to the gradual loss of large and small myelinated fibres as well as unmyelinated fibres. Loss of vibration sensation and proprioception reflect large fibre loss. Impairment of pain, light touch and temperature is secondary to small fibre loss.

The first step to diagnosis is to take a targeted history. Many patients describe a burning sensation or tingling of the feet. This is typical of prominent small fibre damage. Other patients describe an altered sensation that feels as if the feet have been 'wrapped in plastic' or are 'tight'. A person with diabetes may not use the word 'pain'. Some patients describe less specific symptoms such as fatigue, cramping or aching. Numbness is often a late symptom, indicating larger sensory fibre loss.

Symptoms are typically worse at night, and when assessing severity and the need for targeted treatment, it is important to ask the patient if sleep is interrupted by the discomfort. A useful way to help differentiate symptoms of peripheral neuropathy from those caused by peripheral vascular disease is that patients often describe walking around (or standing) as helping the symptoms. In some cases, however, patients with diabetic neuropathy may have sensitivity to pressure or minimal stimuli on the feet (hyperalgesia), but this is maximal in the feet and soles, rather than the calves.[8]

A detailed history may elicit contributing factors such as high alcohol intake, smoking, risks for vitamin B_{12} deficiency or past treatment with chemotherapy. Social isolation is an independent risk factor for ulceration. It is important to note that some patients have a dense sensory neuropathy on examination but have few symptoms.[9] These patients are at high risk of ulceration.

Examination

It is important to carefully examine the feet of any patient newly diagnosed with diabetes, including the soles of the feet and between the toes, as many patients may be unaware of their neuropathy. Indeed, some patients are unaware they have an ulcer until they are examined. In established peripheral neuropathy, the foot may have a distinctive shape, with a high arch, clawed toes (Figure 1) and prominent heads of the metatarsals. Distal motor axonal loss results in atrophy of the intrinsic foot muscles and an imbalance between the strength of toe extensors and flexors. In later disease there can be collapse of the arch of the mid-foot. The foot architecture is altered and pressure on bony prominences can cause calluses. The shearing forces of calluses over bone may lead to ulceration (Figure 2). It is important to look for the presence of calluses that may require podiatry treatment. Any previous amputations of toes should be noted as past amputation is a strong risk factor for future amputations and also indicates the need for regular podiatry review.

It is important to assess loss or reduction of the Achilles tendon reflex as this can be an early sign of peripheral neuropathy. Vibration perception in peripheral neuropathy is easily and reliably tested with a 128 Hz tuning fork (Figure 3a).[10] The tuning fork is placed on the interphalangeal joint of the right hallux. If the vibration is felt it should then be compared with the wrist. A biothesiometer is a more specialised instrument designed to measure accurately the threshold of vibration appreciation. Vibration thresholds increase with age. A threshold greater than 30 to 40 amplitude indicates significantly reduced vibration sense. A biothesiometer is usually available in specialised diabetes or podiatry services.

The 10 g Semmes-Weinstein monofilament has been developed as a simple test for diabetic peripheral neuropathy (Figures 3b and c). The filament is placed on the skin and pressure is applied until the filament bends, which transmits 10 g of pressure. The filament is placed on the plantar aspect of the great toe and heads of the third and fifth metatarsals.[11] Testing in eight to 10 spots is no more accurate than testing three to four places.[12] The reported sensitivity of the monofilament has, however, been variable, with one study showing only 57% sensitivity when compared with nerve

Figures 3a to c. Tools to test for peripheral neuropathy. a (top left). The tuning fork method used to test vibration sensation. b and c (above right and bottom). The 10 g Semmes-Weinstein and other commonly used monofilaments.

FIGURE 3a COURTESY OF PROF TWIGG, Ms McCOSTER, Ms BOLTON, ROYAL PRINCE ALFRED HOSPITAL, SYDNEY, NSW.

conduction studies.[12] As a simple quick test to perform, a positive monofilament result can be useful, whereas a negative result may not exclude peripheral neuropathy.

It is important to palpate the peripheral pulses as peripheral vascular disease often coexists with peripheral neuropathy and can contribute to ulceration and poor wound healing.

Nerve conduction studies are indicated if there is uncertainty about the diagnosis. This may arise if the patient presents with weakness rather than sensory loss, if signs and symptoms are asymmetrical or proximal more than distal, or if there is a rapidly progressive course. Referral of the patient to a neurologist may also be required in these circumstances.

Several validated screening tools are available for peripheral neuropathy. The United Kingdom screening test consists of a simple symptom and examination score (see Table).[13] Although this test is designed for use in a hospital clinic setting, it is also suited to a primary care setting. These screening tools are designed as guides rather than as definitive tests.

Table. United Kingdom screening test for peripheral neuropathy[13]

Symptoms		
Question	**Symptom**	**Score**
What is the sensation? (max 2 points)	Burning, numbness, tingling	2 points
	Fatigue, cramping, aching	1 point
What is the location of symptoms? (max 2 points)	Feet	2 points
	Calves	1 point
	Elsewhere	0 point
Have symptoms awakened person at night?	Yes	1 point
What is the timing of symptoms? (max 2 points)	Worse at night	2 points
	Present day and night	1 point
	Present only during day	0 points
How are the symptoms relieved? (max 2 points)	Walking around	2 points
	Standing	1 point
	Sitting or lying or no relief	0 points
Total symptom score 0 to 2 points = normal; 3 to 4 points = mild neuropathy; 5 to 6 points = moderate neuropathy; 7 to 9 points = severe neuropathy.		
Neurological signs		
Examination	**Result**	**Score**
Achilles tendon reflex	Absent	2 points each foot
	Present with reinforcement	1 point each foot
Vibration sense	Absent or reduced	1 point each foot
Pinprick sensation	Absent or reduced	1 point each foot
Temperature sensation	Reduced	1 point each foot
Neurological signs score 0 to 2 points = normal; 3 to 5 points = mild neuropathy; 6 to 8 points = moderate neuropathy; 9 to 10 points = severe neuropathy.		

Monitoring

People with diabetes should be re-screened at regular intervals due to the progressive nature of peripheral neuropathy. Patients should be re-screened at least annually by examining sensory function as described, by both history taking and examination.

At each clinic visit the patient's feet should be examined for new deformities, infection or ulcers. The patient's footwear should be examined and appropriate footwear should be discussed with the patient. The patient should also be instructed in daily inspection of the feet. A long handled mirror may be necessary for patients with limited mobility. All patients with peripheral neuropathy should be educated in good foot care and referral to a podiatrist should be considered.

Future directions

Nerve excitability testing is a novel noninvasive technique, currently available in some larger centres, which assesses axonal ion channel function and membrane potential in nerves. Abnormalities on testing have been shown to correlate well with nerve function and quality of life parameters in patients with type 2 diabetes, and can detect functional abnormalities before formal nerve conduction testing identifies (usually irreversible) abnormalities.[1]

It is hoped that in people with type 1 diabetes, continuous subcutaneous insulin infusion (or insulin pump therapy) may preserve axonal function.[14]

Conclusion

Many patients have established significant peripheral neuropathy on diagnosis of prediabetes or type 2 diabetes, and many patients with type 1 diabetes are at risk of developing peripheral neuropathy at a young age. This contributes significantly to morbidity and reduced quality of life.

Early detection of peripheral neuropathy is therefore warranted to identify patients who would benefit from tighter glycaemic control and attention to contributing risk factors, such as smoking, vitamin B_{12} deficiency, dyslipidaemia and excessive alcohol consumption. Referral of patients to podiatry services is indicated for patients with significant peripheral neuropathy. **ET**

References

1. Kwai N, Arnold R, Wickremaarachchi C, et al. Effects of axonal ion channel dysfunction on quality of life in type 2 diabetes. Diabetes Care 2013; 5: 1272-1277.
2. Diabetes Control and Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
3. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006; 6: 1294-1299.
4. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; 6: 580-591.
5. Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patients with non-insulin dependent diabetes mellitus. N Engl J Med 1995; 2: 89-94.
6. Arnold R, Kwai N, Lin CS, et al. Axonal dysfunction prior to neuropathy onset in type 1 diabetes. Diabetes Metab Res Rev 2013; 1: 53-59.
7. Pourhamidi K, Dahlin LB, Englund E, Rolandsson. Evaluation of clinical tools and their diagnostic use in distal symmetric polyneuropathy. Prim Care Diabetes 2014; 8: 77-84.
8. Bierhaus A, Fleming T, Stoyanov S, et al. Methylglyoxal modification of $Na_v1.8$ facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med 2012; 18: 926-933.
9. Franse LV, Valk GD, Dekker JH, et al. 'Numbness in the feet' is a poor indicator for polyneuropathy in type 2 diabetic patients. Diabetic Med 2000; 2: 105-110.
10. Meijer JW, Smit AJ, Lefrandt JD, et al. Back to basics in diagnosing diabetic polyneuropathy with the tuning fork! Diabetes Care 2005; 9: 2201-2205.
11. Feng Y, Schlosser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic neuropathy. J Vasc Surg 2009; 3: 675-682.
12. Baraz S, Zarea K, Shahbazian HB, Latifi SM. Comparison of the accuracy of monofilament testing at various points of feet in peripheral diabetic neuropathy screening. J Diabetes Metab Disorders 2014; 1: 13-19.
13. Young MJ, Boulton AJ, MacLeod AF, et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 2: 150-154.
14. Kwai N, Arnold R, Poynten AM, et al. Continuous subcutaneous insulin infusion preserves axonal function in type 1 diabetes mellitus. Diabetes Metab Res Rev 2015; 2 : 175-182.

COMPETING INTERESTS: None.

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