

# Neuropad: early diagnostic test for diabetic peripheral neuropathy

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## KEY POINTS

- Neuropad is a prescribable diagnostic test for peripheral diabetic neuropathy
- available as a 2-pad test pack (1 pad for each foot) at a cost of £6.99
- it is an adhesive pad containing a cobalt II compound and is placed on the first metatarsal
- in the presence of sweat production, *ie* healthy autonomic nervous system, the pad will undergo a blue to pink colour change; incomplete colour change is indicative of nerve damage
- in clinical trials, the sensitivity and specificity of Neuropad for diabetic neuropathy was comparable to that of established secondary-care diagnostic tests
- time to complete the colour change was associated with the severity of the neuropathy



**Diabetic foot syndrome is a significant cause of morbidity in patients with diabetes, and early diagnosis of peripheral neuropathy can improve prognosis. In this New product review Professor Malik describes Neuropad, a new prescribable diagnostic test for peripheral diabetic neuropathy.**

The diabetic foot refers to the foot-related complications associated with diabetes mellitus, in particular foot ulceration, which is the leading cause of hospitalisation among diabetic patients.<sup>1</sup> The most important cause of foot ulceration is diabetic peripheral neuropathy<sup>2</sup> and is defined as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes'. It is noteworthy that foot ulceration often develops due to loss of sensation and hence an 'absence of symptoms'.

The incidence of amputation is significantly higher in patients with diabetes than in nondiabetic patients (one study showed that a 13.1-fold increase in the amputation rate in patients

with diabetes<sup>3</sup>), and more than 1 in 10 foot ulcers result in an amputation.<sup>4</sup>

Importantly, the majority of patients with diabetes undergoing amputation have an ulcer, and in fact diabetes is the most common cause of nontraumatic amputation in the UK, with 5000 diabetic patients undergoing an amputation every year.<sup>4</sup>

Screening and early identification of patients at risk of developing the diabetic foot syndrome offers a vital opportunity for diabetic patients to make behavioural changes to reduce the risk of unperceived trauma and identify those patients who should undergo more intense intervention including improved glycaemic, blood pressure and lipid control.<sup>5,6</sup>

## Consequences of nerve dysfunction and damage

Diabetic peripheral neuropathy is traditionally subdivided into lesions affecting the somatic (sensory and motor nerves) and the autonomic nervous systems. Sensory neuropathy leads to a loss of sensation initially in the toes but progressing more proximally to the entire foot and lower leg, which can predispose patients to unperceived trauma and facilitate the development of foot ulceration.

Motor neuropathy contributes to muscle atrophy and deformities, which leads to abnormally high forces and shear stress – both precursors to wound formation.

Both large- and small-diameter nerve fibres are implicated in neu-

ropathy. Sensory neuropathy is mediated by large nerve fibres, and small fibres not only mediate pain but also play a vital role in the pathogenesis of foot ulceration via their function within the peripheral autonomic nervous system. Autonomic innervation of sweat glands and dermal blood vessels alters tissue hydration and blood flow, both important in the genesis of breakdown of skin integrity that leads to ulceration.

Absence of reliable symptoms and a high prevalence of asymptomatic disease make foot screening essential. National Institute for Health and Clinical Excellence (NICE) guidelines state that patients with type 2 diabetes should have their feet examined annually.

### Diagnosis

A range of tests are available in both primary and secondary care for the diagnosis of somatic diabetic neuropathy (see Table 1). However, in routine primary care there remains a need for a simple and reliable patient assessment for diabetic peripheral autonomic neuropathy.<sup>7</sup>

Examination of foot sensation is essential and is achieved by using a 10g monofilament or 128MHz tuning fork to assess loss of touch and vibration sense, respectively. Additionally an assessment of foot pulses and inspection for foot deformity and appropriate footwear is important.

Each patient is classified in terms of their risk of ulceration as follows: low current risk, increased risk, high risk, and those with a foot ulcer. Low-risk patients should undergo annual review, those at increased risk are reviewed six monthly, and those at high risk every one to three months.

Test	Measures	Advantages	Disadvantages
<b>Primary care</b>			
<i>Monofilament</i>	assesses large-fibre sensory neuropathy	inexpensive readily available	relies on subjective response of patient no agreement on number of sites to test
<i>Vibration sense</i>	assesses large-fibre sensory neuropathy	inexpensive	relies on subjective response of patient requires key skills to reliably test whole foot
<b>Secondary care</b>			
<i>Nerve conduction studies (NCS)</i>	early diagnosis of nerve damage	accurately measures large-fibre impairment	not available in primary care requires special equipment and expert personnel does not assess small fibres
<i>Vibration perception threshold (VPT)</i>	determines large sensory fibre impairment	fairly accurate quantifies loss of vibration sensation	secondary care, only occasionally used in primary care dependent on patient response
<i>Intraepidermal nerve fibre density (IENFD)</i>	skin biopsy	demonstrates early damage to small fibres	invasive procedure difficult to perform need specialist lab to perform analysis
<i>Quantitative sudomotor axon reflex test (QSART)</i>	assesses autonomic neuropathy by measuring sweat reflex	accurate	time consuming requires specialised equipment expert personnel and training

**Table 1.** Advantages and disadvantages of primary- and secondary-care tests for the diagnosis of diabetic peripheral neuropathy

However, primary-care tests, namely monofilament and vibration sensitivity, which test large sensory nerves, rely on the subjective response of the patient

and only detect established neuropathy. Additionally, the reliance on patient feedback risks producing both false negatives and false positives, making the



**Figure 1.** In the presence of sweat production Neuropad will undergo a blue to pink colour change; in patients with nerve damage, insufficient sweat levels will fail to trigger the colour change and early nerve damage will only produce a partial colour change (centre)

task of risk stratification difficult, and diagnostic errors are potentially very costly.

Patients, particularly in a secondary-care setting, may undergo more sophisticated assessment avoiding the risk of a subjective response, with tests such as nerve conduction studies, skin biopsy and the quantitative sudomotor axon reflex test (QSART). However, such tests are costly and impractical in the primary-care environment.

#### **Economic implications of poor neuropathy diagnosis**

Diabetic foot syndrome accounts for a significant proportion of the cost of diabetes care due to long periods of hospitalisation, rehabilitation, recurrent foot ulceration and amputation. It has been estimated that one ulcer costs £5200 to treat annually.<sup>9</sup>

In patients with mild, moderate and severe clinical neuropathy both the monofilament and the tuning fork test fail to diagnose many patients with definite neuropathy.<sup>7</sup> The monofilament misdiagnoses 29 per cent of patients and tuning fork 55 per cent, compared to only 9 per cent of patients being misdiagnosed with nerve conductive studies (NCSs). Misdiagnosis of neuropathic risk

therefore presents considerable and avoidable cost.

#### **Neuropad**

Sweat glands are under the control of the unmyelinated C-fibres of the autonomic nervous system, therefore an assessment of sweat gland function may serve as a proxy for diabetic autonomic neuropathy.

Neuropad, a small adhesive pad containing a cobalt II compound, is a novel diagnostic test that measures the moisture status of the foot, which may act as a surrogate for peripheral autonomic neuropathy. Sweat production is indicated by means of a blue (dry state) to pink (dermal foot perspiration) colour change (see Figure 1).<sup>9</sup> A result is visible within 10 minutes.

Neuropad has been validated against both primary- and secondary-care diagnostic tests. The clinical efficacy of this simple diagnostic test has been determined in over 40 clinical studies, involving more than 1000 diabetic patients.

The sensitivity of Neuropad is comparable with NCS and the neuropathy disability score (NDS), which significantly exceeds that seen with the monofilament and tuning fork tests. Furthermore,

Neuropad has good sensitivity and specificity in the detection of patients with intermediate or high risk for foot ulceration determined by comparison with neurological deficits and vibration perception threshold (VPT).<sup>11</sup>

In a study of 154 patients with type 2 diabetes,<sup>11</sup> neuropathy was diagnosed clinically using NDS, and VPT was measured with a neurothesiometer with values >25 volts classified as abnormal. The sensitivity of Neuropad for established neuropathy was 98 per cent and specificity 67 per cent compared to a sensitivity and specificity for VPT of neuropathy of 79 and 86 per cent, respectively. Furthermore, there was a significant correlation between the time to colour change of the Neuropad and VPT.

In a study of 120 patients with type 2 diabetes, Neuropad had a validity comparable to that of NCS for the diagnosis of diabetic neuropathy.<sup>12</sup> The sensitivity of Neuropad for clinical neuropathy was 95.2 per cent and its specificity was 67.6 per cent, which was comparable to 94 and 62.1 per cent, respectively, for NCS. Time to complete colour change was again associated with the severity of neuropathy.

Recently, in a study to assess how well Neuropad performs

against the gold-standard measure of early neuropathy – reduction of intraepidermal nerve fibre density (IENFD) – 57 diabetic patients underwent a skin biopsy and IENFD assessment.<sup>13</sup> Patients with a normal Neuropad result had a nonsignificant reduction in IENFD, while patients with a patchy or abnormal result had a significant reduction in IENFD.

### Neuropad – use in practice

The Neuropad test kit consists of two tests – one for each foot – detailed instructions and a wipe for cleaning the foot after the test. It is simple to use, takes 10 minutes to assess and may be applied at home by the patient or in the clinic during routine annual assessments.

Prior to use, shoes and socks are removed and the foot is allowed to acclimatise for five minutes to reduce the impact of ambient temperature. The pad is placed on the first metatarsal of both feet after callus removal, but may be placed further round the foot if callus cannot be removed.

As Neuropad appears to detect neuropathic deficits before monofilament and vibration perception testing, it has potential as a screening test for early neuropathy and referral onward to specialist podiatry care. It may also be particularly useful in patients with communication or language difficulties who may not respond accurately to tests such as the monofilament.

### Conclusion

Current primary-care tests for neuropathy are subjective and therefore prone to false negative and positive results. Neuropad is a non-subjective test with a sensitivity, specificity and reliability comparable to established secondary-care diagnostics.<sup>10-14</sup> Thus Neuropad could allow patients with neuropathy to be diagnosed earlier than is possible with current tests, allowing clinicians to target those patients who should undergo more intense multifactorial intervention.<sup>4,5</sup>

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