Point-of-care devices for detecting diabetic polyneuropathy

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Clinical Question:

In Primary Care, what is the accuracy and utility of devices available for detecting diabetic polyneuropathy in patients with diabetes mellitus?

Background, Current Practice and Advantages over Existing Technology:

Diabetic peripheral neuropathy (DPN) is defined as peripheral neuropathy in a patient with diabetes, with no other identifiable cause (1). DPN can be a debilitating and life changing complication of diabetes that can have severe impacts on the patient's independence and cost implications to the NHS. Detection and regular follow up of diabetic neuropathy is necessary to allow for patient education to recognise and treat any complications of diabetic neuropathies, including trauma, infection and ulcers (2). This is necessary to delay or prevent limb threatening complications. Figures show that in 84% of diabetic patients who had undergone a lower limb amputation, had preceding foot ulcers, which reveals the importance of treating diabetic neuropathy complications (3). Accurately diagnosing diabetic neuropathy would require skin biopsy as the gold standard which is impractical in routine practice. Current practices in primary care include eliciting signs and symptoms of DPN and performing a monofilament test to test for sensory neuropathy. The current Nice guideline (NICE Guidance NG19) (4) recommends the following for assessing patients with type 2 diabetes in primary care for lower limb neuropathies: Testing of foot sensation using 10g monofilament or vibration, palpation of foot pulses, inspection for any foot deformity and inspection of footwear.

This mainly tests for large fibre symmetrical peripheral neuropathy and normally picks up symptoms further along the disease process. Studies have shown that small fibre neuropathy may be the earliest indicator for diabetic neuropathy (5), but there is currently no standardised test in the primary care setting to test for early stages of peripheral neuropathy. This in turn can lead to delays in targeting those patients who need more vigorous glucose control and more regular follow ups. In addition to being an insensitive test for identifying early stages of DPN, monofilament testing is subject to operator variability, patient subjectivity and co-operation. A systematic review had revealed that sensitivity for monofilament testing ranged from 41% to 93% and specificity ranged from 68% to 100% but no meta-analysis could be performed due to the heterogeneous nature of the studies (6).

Importance:

Diabetes mellitus is a highly prevalent chronic condition. According to the NHS Information Centre in 2013 the prevalence in the UK was 5.8% and diabetes is in the top five highly prevalent chronic conditions in UK. DPN is one of the most common complications of diabetes mellitus (1); up to 50% of diabetic patients can suffer from polyneuropathy and 50% of these patients are asymptomatic (7). Diabetic neuropathy can lead to complications such as lower limb ulceration and, in more advanced cases, lower limb amputation. DPN is the most common cause of hospitalisation due to complications secondary to diabetes and DPN is the leading cause of non-traumatic lower limb amputation (2).

There have been many studies looking into the screening process of diabetic neuropathy. The majority of the tests have poor sensitivity and specificity for identifying early stages of DPN. The review by Cornblath (8) has highlighted that there is some degree of inconsistency between the different modalities of quantitative testing methods. Quantitative testing for thermal and vibratory perception are not as precise as nerve conduction studies (NCS), which is why this form of quantitative measurement remains the gold standard prior to nerve biopsy. It is currently not feasible for patients to all undergo NCS as they are expensive and require specialists to perform.

Details of Technology:

In this report we have looked at a number of devices that are currently available to diagnose diabetic peripheral neuropathy. Based on previous research and current understanding of diabetic peripheral neuropathy, the features of an ideal device are:

1) Ease of use
2) Little to no operator variability
3) Quantitative measures
4) Patient involvement – the degree to which the measurement is based on patient answers, such as reporting when they feel a cold burst of air/or feel light touch

These measures were used to assess some of the devices available to diagnose diabetic polyneuropathy in the primary care setting, based on the current available evidence. However the majority of current evidence identified in this report, was generated in non primary care setttings. The modality tested by each device is listed in the table below. Large fibre function and vibration sense are the most sensitive modalities to test, and testing vibration sense can be used to identify early stage disease (9-11). Nerve conduction studies with vibration sense used together may be the most sensitive method of identifying early neuropathic disease (12).

Table 1. List of Devices

Device	Function tested	Patient involvement	Measurement	Ease of use
Neuroquick (Schweers, Meerbusch, Germany)	Thermal	Subjective	Airflow detection	Easy to use
Vibratip (McCallan Medical)	Sensory	Subjective	Vibration sense	Easy to use

Monofilament 10-g	Sensory	Subjective	Light touch	Easy to use
Tactile circumferential Discriminator (TCD)	Sensory	Subjective	Touch sensation	Easy to use
Steel ball bearing	Sensory	Subjective	Touch	Easy to use
Biothesiometer	Sensory	Subjective	Vibration sense	Requires software
NC-stat (Neurometrix, Waltham, USA)	Sensory	Objective	Multi component	Easy to use
Neuropad, (Trigocare International, Germany)	Sudomotor	Objective	Colour change	Easy to use
Sudoscan, (Impeto Medical, Paris, France)	Sudomotor	Objective	Thermal	Requires software

In this report we will be focussing on the devices providing objective measurements, which are Sudoscan, Neuropad and NC-Stat DPNcheck. The reasons for excluding the other devices are due to the use of qualitative measurements, which studies have shown to be a less accurate method of diagnosing DPN.

The Neuropad (Trigocare®), Sudoscan (Impeto Medical®) and NC-stat (Neurometrix®) are devices that measure irregularities in the peripheral nerve function.

The Neuropad measures sweat production based on a colour change in a cobalt II compound from blue to pink. When the colour changes from blue to pink, there is normal sudomotor function and where the colour stays blue or appears patchy it identifies reduced sudomotor function. The time taken for the colour change from blue to pink is measured. The time usually taken for colour change is about ten minutes and patients need to remove their socks and shoes to allow the foot to acclimatise and wait five minutes before using the device (13).

Sudoscan involves a computer device with a touchscreen monitor and stainless steel metal plates to place both feet upon and a second set to place hands upon. The patient's details are then fed into the computer device using a touchscreen monitor and a graph is produced that measures the sudomotor function with a reading that is produced in under three minutes (14, 15) following the acclimatisation period.

The NC-stat DPN check is a handheld device that is placed over the skin overlying the sural nerve and the sural nerve conduction velocity and the sensory nerve action potential is measured. This is displayed as numbers and the threshold for detecting abnormalities is pre-defined. Based on these values patients can be screened for diabetic neuropathy. In order to locate the sural nerve, operators are trained in identifying this, and this is missing in a small number of people, and therefore the NC-Stat DPN Check cannot be used for these patients.

Patient Group and Use:

- Routine assessment of patients with diabetes mellitus to detect diabetic neuropathy in a primary care setting

Previous Research:

Accuracy compared to existing technology

Neuropad

The accuracy of this device was investigated by Papanas et al (16) . This study was a cross-sectional cohort diagnostic accuracy study with 251 consecutive adults with type 2 diabetes who were recruited from diabetes outpatient clinics in Greece. In this study the Neuropad was compared to the neuropathic disability score, which comprises of history and examination of multiple modalities including ankle reflexes, sensation, pin-prick and temperature. The prevalence of DPN in this study population would be significantly greater than in the general population seen in primary care. However given that this device would likely only be used in patients diagnosed with diabetes in primary care, then the prevalence may be more similar to the population in this study. This study does not however state whether the patients in this study population suffered with difficult to control diabetes, or patients who were more complicated than the general primary care population. The study reported the following percentages sensitivity, specificity and positive (PPV) and negative (NPV) predictive values:

Degree of DPN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Mild	95 (92-97)	75 (36-94)	99 (98-100)	21 (9-43)
Moderate	91 (85–95)	96 (92-98)	96 (91-98)	92 (87-95)
Severe	91 (82-96)	95 (92-97)	84 (72-91)	98 (95-99)

One study of 57 diabetic patients (17) assessed the accuracy of the Neuropad compared to established measures of somatic and autonomic neuropathy i.e. to the NDS, neuropathic symptoms score, cold detection, heat as pain perception threshold visual analogue score and deep breathing heart rate variability and intra-epidermal fibre density.

The sensitivity of an abnormal Neuropad response in identifying a clinical neuropathy was 85% with a negative predictive value of 71%, a specificity of 45% and a positive predictive value of 69%. The results also showed statistically significant correlations between the Neuropad test and cold detection threshold ($p=0.03$), deep-breathing heart rate ($p<0.001$) and heat as pain perception ($p=0.043$). There was also correlating reduction in intraepidermal nerve fibre density in patients identified as having an abnormal Neuropad test ($p=0.02$).

A multicentre study by Manes et al (18), assessed the diagnostic utility of Neuropad on 1010 patients with type 2 diabetes from 5 diabetic clinics. Patients were divided into two groups, one with sudomotor dysfunction, which had older patients, and a second group of patients without sudomotor dysfunction. The following figures were reported:

DPN	Sensitivity	Specificity	NPV
Overall nerve fibre dysfunction – abnormal (patchy/blue)	94.9	70.2	98.1
Small fibre dysfunction (patchy readings)	85.6	71.2	93.3
Overall nerve fibre dysfunction – abnormal (blue)	64	96	91
Small fibre dysfunction (abnormal readings)	52	96	85

In the study by Ponirakis et al (19) the sensitivity and specificity of Neuropad against various diabetic neuropathy diagnostic tools were assessed. This study had 127 participants, 38 with diabetic polyneuropathy. The Neuropad results were blindly interpreted by independent clinicians. This study compared the Neuropad against other screening methods as reference standards and showed variable sensitivities and specificities. The table below shows the percentage sensitivities and specificities when the Neuropad was compared to different modalities:

Comparator modality	Sensitivity	Specificity
Neuropathy Disability Score (NDS)	70	50
Vibration perception threshold (VPT)	83	53
Peroneal motor nerve conduction velocity	81	54
Corneal fibre length	83	80
Neuropathic symptoms	78	60

In a study by Ponirakis et al (20) 110 patients with type 1 and type 2 DM underwent assessment with the Neuropad, and underwent multiple other assessments as highlight below as reference standards. The percentage sensitivities and specificities of the Neuropad with each variable being used as a reference standard are highlighted below. For example, where NDS was used as the diagnostic standard for diagnosing DPN, the sensitivity of the neuropad when using categorical cut offs was 69%. Patients were recruited from a Manchester diabetes centre; of the 110 patients recruited 84 suffered from type 1 diabetes and 26 suffered from type 2 diabetes.

Variables	Continuous		Categorical	
	Sensitivity	Specificity	Sensitivity	Specificity
	Large fibre assessments			
NDS (>2)	71	58	69	62
VPT (>14V)	80	71	70	57
SNAP (<3µV)	85	83	100	55
SNCV (<43m/s)	66	61	61	59
PMNAP (<2 µV)	67	54	62	50
PMCV (<42m/s	62	28	60	53
	Small fibre assessments			
IENFD (<4no./mm)	65	54	56	51
CNFD (<24no./mm^2)	88	78	89	63
CNBD (<18no./mm^2)	83	72	100	47
CNFL (<14mm/mm^2)	89	75	90	50
DB-HRV (<10 beats/min)	91	83	82	59
WPT (>42^oC)	75	60	69	33

NDS – neuropathy disability score, VPT – vibration perception threshold, SNAP – sural nerve action potential, SNCV – sural nerve conduction velocity, PMNAP – peroneal motor nerve action potential, PMNCV – peroneal motor nerve conduction velocity, IENFD – intraepidermal nerve fibre density, CNFD – corneal nerve fibre density, CNBD – corneal nerve branch density, CNFL – corneal nerve fibre length, DB-HRV – deep breathing heart rate variability, WPT – warm perception thresholds

<u>NC – Stat DPN Check</u>

In a study of 72 consecutive patients with diabetes from a diabetes and neuropathy outpatient clinic, patients were evaluated concurrently with conventional nerve conduction studies as the reference

standard and the NC-Stat DPN Check point-of-care device for sural nerve function (21). The reference standard used in this study was the counterpoint device that measures nerve conduction according to the standards of the American Association for Neuromuscular and Electrodiagnostic Medicine. In the results of this study the sensitivity was calculated at 92% and the specificity at 82% , with a PPV of 92% and NPV of 82%.

Another study by Sharma et al in 2014 (22) also assessed the accuracy of the NC-stat DPN check. In this study the point-of-care device was compared to the LDI_{FLARE} technique. In this study a total of 80 healthy controls and 162 patients, 80 with type 1 and 82 with type 2 diabetes were recruited from the Diabetes outpatient clinics at Ipswich hospital, UK. It appears that all patients underwent a NDS score, POCD testing and LDI_{FLARE} testing. This study showed a good correlation between the LDI_{FLARE} and the POC device.

	AUC			
	No DPN	Mild DPN	Moderate DPN	Severe DPN
LDI_{FLARE}	0.901	0.768	0.767	0.964
SNCV	0.896	0.743	0.814	0.907
SNAP	0.868	0.703	0.804	0.869

SNCV – Sural nerve conduction velocity, SNAP – Sural nerve amplitude
AUC – Area under curve

In a study of 44 patients with type 1 and type 2 diabetes (23), the DPN Check was used to screen for diabetic neuropathy, using nerve conduction studies (NCS) as the reference standard. The percentage sensitivities and specificities are highlighted in the table below:

	Sensitivity	Specificity
SNCV	94	82
SNAP	88	94
Identification of DSP	95	71

DSP – diabetic sensorimotor polyneuropathy

Sudoscan

In a study by Casellini et al (14), 83 diabetic patients and 210 healthy controls underwent neuropathy impairment score, quantitative autonomic function testing and quantitative sensory testing, to test the accuracy of sudoscan. The percentage sensitivity, specificity and predictive values are highlighted below, where the diagnostic accuracy of sudoscan was measured against neurological impairment score:

	Sensitivity	Specificity	PPV	NPV
Hands	78	85	61	93
Feet	78	92	74	93

A study by Smith et al (15) in 2014 also tested the accuracy of the sudoscan device. In this study 55 patients with suspected diabetic distal neuropathy and 42 controls, without diabetes, underwent the Utah Early Neuropathy Scale (UENS), a physical exam scale (diagnostic standard in this region) and

sudoscan testing. Participants were also offered skin biopsy. Patients with known diabetic distal neuropathy underwent quantitative sudomotor axon reflex testing and nerve conduction studies. The sensitivity of the sudoscan measuring electrochemical skin conduction was 77% and specificity was 67% when using the UENS as the gold standard, with a PPV of 59% and a NPV of 83%.

In a study by Eranki et al (24), 309 patients with type 2 diabetes at a follow-up centre in India were recruited and underwent VPT (vibration perception threshold) testing using a biothesiometer and sudoscan measurements. The sensitivity was 82% and the specificity was 61% for using the sudoscan to detect microvascular complications in type two diabetes.

The table below summarises the percentage sensitivities and specificities from the above studies; those marked with an asterisk are for detection of mild DPN where quoted, otherwise overall sensitivities and specificities have been quoted

Device	Study		Sensitivity	Specificity	AUC
Neuropad	Papanas, 2011		95*	75*	
	Quatrrini 2008		85*	45*	
	Manes 2014		64	96	
	Ponirakis 2014 (corneal nerve length)		83	80	
NC-Stat	Perkins 2006		92	82	
	Sharma 2014	SNCV			0.743*
		SNAP			0.703*
	Lee 2014	SNCV	94	82	
		SNAP	88	94	
Sudoscan	Casellini 2013		78	86	
	Smith 2014		77	67	
	Eranki 2013		82	61	

*For the detection of mild DPN

Impact compared to existing technology

No studies were identified in the search strategy for this review that looked at clinical outcomes during the use of POC devices detecting diabetic polyneuropathy. Furthermore there were no studies that were conducted in a primary care GP setting. A study looking at the use of point-of-care devices in the community pharmacy setting was performed (26). This study utilised the NC-Stat DPNcheck device for patients using the pharmacy willing to undergo point-of-care tests to check Hba1c and diabetic neuropathy. Pharmacists were able to use the readings of the Hba1c test and the NC-Stat DPNcheck readings to stage the patient's diabetic neuropathy and counsel patients to safeguard their limbs. This study showed that the NC-Stat DPNcheck was an easy to use device that could lead to an increase in patient education in the community. However there was no long term follow-up to see if there was an impact following this education.

Usability

From the studies above it appears that all the devices came with instructions on how to use the device and the clinicians were trained in their use. The sudoscan was a computer-based programme,

whereas the Neuropad and the NC-stat DPN Check were hand-held devices. The Neuropad depended on appreciations of colour change from blue (normal) to pink (abnormal), whereas the NC-stat DPN check gave objective readings for sural nerve conduction velocity (SNCV) and sural nerve amplitude (SNAP).

Guidelines and Recommendations

NICE guideline CG 10: Type 2 diabetes foot problems: Prevention and management of foot problems. 2004. An update is due to be published in August 2015. (http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0659).

Research Questions:

1) Diagnostic accuracy of these devices in primary care
2) The usability of point of care devices for detecting DPN in primary care setting
3) Clinical outcomes in patient management following use of POC devices for detecting DPN

Conclusion:

The findings in this report suggest that the specificities for the devices were generally relatively low. The sensitivities quoted were better for the screening devices, however they were lower when looking at mild DPN. In general if used as a screening tool, it is important to be able to rule out patients who do not have the condition and therefore products with a higher sensitivity may be of more clinical relevance.

Studies have shown that nerve conduction studies are the most objective measure of nerve function (25). The studies reviewed in this report suggest that the NC-Stat device appears to have the better of the sensitivities, and also shows quantitative measures for the conduction velocity and sural nerve amplitude. It also gives cut-off ranges for normal and abnormal readings and is an easy to use device. The limitations to this device are that patients who have an absent sural nerve will not be able to utilise this device. However there is currently insufficient evidence to inform the use of these devices in primary care.

Where patients can be identified earlier showing signs of diabetic polyneuropathy, they can have shorter follow up periods, education in how to detect and manage trauma, infection and ulceration of their feet and earlier presentation to healthcare services if there are any complications to their foot care. This will hopefully delay the progression to severe lower limb complications and avoid amputation.

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