THE UTILITY OF A POINT-OF-CARE SURAL NERVE CONDUCTION DEVICE FOR DETECTION OF DIABETIC POLYNEUROPATHY: A CROSS-SECTIONAL STUDY

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ABSTRACT: *Introduction*: Rapid and accessible methods for diagnosing diabetic polyneuropathy (DPN) have been developed, but not validated, in large cohorts of people with diabetes. *Methods*: The performance of a point-of-care device (POCD) was studied in 168 patients with type 2 diabetes, estimating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared with conventional sural nerve conduction studies (NCS). *Results*: A POCD amplitude limit of 6 μV increased the sensitivity (96%) and NPV (98%), but decreased the specificity (71%) and PPV (54%) compared with the 4-μV limit, which had values of 78%, 92%, 89%, and 71%, respectively. POCD on both legs showed better performance than on 1 leg. POCD amplitudes and conduction velocities correlated significantly with conventional sural NCS, but POCD values were underestimated compared with NCS. *Discussion*: The POCD may be used as a suitable screening tool for detection of DPN. Patients with abnormal and borderline results should undergo conventional NCS.

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Detection of diabetic polyneuropathy (DPN) at an early stage is important for preventing complications such as foot ulceration and limb amputation, thereby decreasing both short- and long-term morbidity from diabetes.[1] Electrophysiological methods, in particular nerve conduction studies (NCS), are valuable tools in diagnosing DPN to identify and quantify the involvement of large sensory and motor fibers and for classifying the neuropathy as primarily axonal or demyelinating.[2] NCS have long been considered the "gold standard" for diagnosing DPN affecting large nerve fibers. Yet, conventional NCS are time-consuming and expensive and, consequently, only performed in a limited number of patients with diabetes.[3] Thus, the diagnosis of DPN is often arrived at after a clinical examination or simple sensory examination with a monofilament or a 128-Hz vibration tuning fork by a primary care practitioner or diabetes specialist.[4,5] A more rapid and accessible method for diagnosing DPN, providing quantitative results similar to those provided by conventional NCS, would be ideal. For this purpose, a point-of-care device (POCD) for sural NCS was developed.

The POCD is a hand-held, portable, and easily used device and does not require extensive training of the examiner.[6–8] Investigations of the clinical utility of the POCD compared with NCS have been limited to studies of smaller cohorts of healthy subjects and patients.[6,7] Thus, validation of the accuracy and utility of this device in larger study samples is needed. The present study aimed to explore the utility and accuracy of the POCD compared with conventional NCS in a large cohort of people with screen-detected type 2 diabetes.

METHODS

Participants. The study cohort was derived from 200 - unselected participants from the Danish arm of the Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (the ADDITION trial), which has been described in detail elsewhere.[9,10] Briefly, ADDITION-Denmark enrolled participants 40–69 years of age with previously undiagnosed diabetes via stepwise screening in primary care in the period 2001–2006. In Denmark, 1,533 participants were enrolled, and the general practitioners were randomized to provide either routine care or intensive multifactorial, target-driven care for diabetes until the trial was completed in 2009.[10,11] After closure of the ADDITION trial, participants were followed observationally in the ADDITION study via questionnaires, registers, and by a clinical examination carried out at 5 study sites between 2015 and 2016, that is, 13 years after the trial baseline.[12,13] Two hundred

Abbreviations: ADDITION, Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (trial); AUC, area under the curve; CV, conduction velocity; DPN, diabetic polyneuropathy; NCS, nerve conduction studies; NPV, negative predictive value; POCD, point-of-care device; PPV, positive predictive value; ROC, receiver operating characteristic; SNAP, sensory nerve action potential

Key words: diabetic polyneuropathy, POCD, nerve conduction study, point-of-care nerve conduction device, sural nerve

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participants were examined at the study site in Aarhus. This study was approved by the Committee on Health Research Ethics in the Central Denmark Region (file no. 20000183 and 1-10-72-63-15) and by the Danish Data Protection Agency (file no. 2005-57-0002, ID185). All study participants signed an informed consent document to participate in this study.

NCS. All NCS were performed using Keypoint.Net electromyography equipment (Dantec, Skovlunde, Denmark). In all participants, sensory NCS of the sural nerves were assessed bilaterally using surface electrodes. In addition, sensory and motor NCS of the median nerve as well as motor NCS of the peroneal and tibial nerves were assessed on the right side. The left side was assessed if the right side could not be examined due to, for example, amputation or a skin lesion. The ulnar nerve was included instead of the median nerve when electrophysiological signs of median neuropathy at the wrist were present.

For all sensory and motor NCS recordings, disposable pregelled surface electrodes (Ag/AgCl) with a recording area of 15 × 20 mm or ring electrodes were used. The skin temperature was maintained between 32° and 36°C by a heating lamp. All sensory nerve results used in this study represented an average at least 20 stimuli. All examinations were performed by the first author (M.A.K.), who is experienced in performing NCS and who was blinded to the POCD recordings performed by another person.

Sural Nerve Antidromic Surface Recording. Surface sural sensory nerve action potential (SNAP) was assessed by recording behind the lateral malleolus and stimulating 13 cm proximally lateral to the edge of the Achilles tendon[14] using a surface bar stimulator (Dantec 13L36) with a distance of 23 mm between the cathode and the anode. The amplitude was measured peak to peak, and the latency was calculated from stimulus onset to the first positive peak for the determination of CV.[14]

Peroneal/Tibial Motor and Median/Ulnar Sensory and Motor NCS. Peroneal nerve motor NCS were performed by supramaximal stimulation at the ankle and distally to the capitulum fibulae and recording from the extensor digitorum brevis muscle. Tibial nerve NCS were done by stimulation at the medial malleolus and popliteal fossa and recording from the abductor hallucis muscle. Median motor NCS were performed by supramaximal stimulation at the wrist and the elbow and recording from the abductor pollicis brevis muscle. Median sensory NCS were performed by supramaximal stimulation at the wrist and recording at the second digit. For the ulnar motor nerve, stimulation was applied at the wrist and 3 cm below the elbow and recording from the abductor digiti minimi muscle. Ulnar sensory NCS were performed by stimulation at the wrist and recording at the fifth digit. Distal motor latency, CV, F-wave latency, and compound muscle action potential amplitude were the evaluated motor NCS parameters. For sensory NCS, CV and SNAP amplitude were measured.

DPN Diagnosis by Use of NCS Sum *Z*-Score. For all NCS examinations, age- and height-matched normative reference laboratory values were used, defining *Z*-scores for the assessed nerve parameters. Values beyond ± 2 SD from the mean were considered abnormal. From NCS, each patient was categorized as having DPN or not, using a sum of *Z*-scores from the average of 6 of the following parameters of NCS for each participant: peroneal motor CV; tibial motor CV; tibial minimum F-wave latency; sural SNAP amplitude; median or ulnar motor CV; and median or ulnar minimum F-wave latency. These nerves and parameters were selected according to the Dyck criteria.[15] If the sum *Z*-score was > 2, the participant was considered to have DPN (DPN^+). Participants with a sum *Z*-score of ≤ 2 were considered not to have DPN (DPN^-).

POCD Sural Nerve Recordings. Sural nerves were examined bilaterally with the POCD (NC-stat/DPNCheck; Neurometrix, Inc., Waltham, Massachusetts) by a nurse who was blinded to the results of the conventional NCS examinations. The nurse was trained for 2 days. The device was placed on the skin posterior to the lateral malleolus over an area corresponding to the anatomical distribution of the sural nerve. The POCD is comprised of a single hand-held unit measuring CV and amplitude of the SNAP with a single-use biosensor at a fixed distance of 92.2 mm from the stimulating probes at the end of the device. According to the automated protocol, the sural nerve was orthodromically stimulated 4–16 times within 10–20 seconds, when the POCD was activated by the examiner. The number and the duration of the stimuli varied by the strength of the sural nerve signal detected by the biosensor. This biosensor contains a large area for stimulation and recording without the need for careful positioning of the device by the examiner. The device measures skin temperature and corrects the CV for skin temperature between 23° and 28°C by using a built-in infrared thermometer. The response is recorded as zero if the amplitude of the sensory action potential is measured at less than 1.5 μV or is undetectable.[8]

DPN with POCD. POCD results were evaluated against the reference values provided for the device (abnormal result defined by amplitude ≤4 μV or conduction velocity ≤40 m/s). The accuracy of an amplitude cut-off of ≤ 6 μV was also examined. Because DPN is a symmetrical disease, a diagnosis of DPN requires abnormal recordings by the POCD bilaterally. The exception to this is that we considered a unilateral recording as valid for a DPN diagnosis if only 1 leg was accessible for recordings, such as in cases of amputation or bandaging of the other leg. We also aought to determine whether examining only 1 leg provided the same results as examining both legs.

Data Analysis. Characteristics of participants according DPN status (DPN^+ or DPN^-) were compared using Kruskal–Wallis and chi-square tests, as appropriate. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the performance of the POCD (normal or abnormal) using the cut-offs provided for the device against NCS (DPN^+ or DPN^-). This was done using: (1) mean values of up to three POCD measures bilaterally; (2) only the first POCD measure bilaterally; and (3) only the first POCD measure from each leg. In addition, we evaluated the performance of the POCD when a cut-off of 6 μV was taken, and when the borderline results (amplitude > 4 μV and ≤6 μV) were disregarded with unchanged cut-off levels for CV. The performance of POCD for these clinical groups was also examined by calculating the sensitivity, specificity, PPV, and NPV against NCS (DPN^+ or DPN^-). Moreover, the amplitude and CV of the POCD against NCS sum-score–determined DPN^+ or DPN^- were evaluated with a receiver operating characteristic (ROC) curve analysis, by obtaining the area under the ROC curve (AUC). Linear regression analyses were performed to assess the correlation between POCD and NCS

amplitude and CV of the sural nerve. Agreement between amplitude and CV as measured by the POCD and NCS was determined by Bland–Altman plots. A normal distribution of data was determined based on Q–Q plots and histograms. Data not following the normal distribution were log-transformed. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Statistics version 20.0 (IBM, Armonk, New York) and Stata release 14.2 (StataCorp LP, College Station, Texas).

RESULTS

Participants' Characteristics. Of the 200 participants with type 2 diabetes, NCS could not be performed in 22 of them due to discomfort, and POCD recordings were not completed in 10 participants due to discomfort or lack of time, leaving a cohort of 168 participants available for study. Of these, 45 (27%) were diagnosed with DPN (DPN^+) and 123 (73%) were determined not to have DPN (DPN^-) using a NCS sum-score of *Z*-scores from 6 parameters derived from 4 different nerves. Participants' characteristics by DPN status are shown in Table 1. DPN^+ participants were more dysglycemic, taller, and heavier than DPN participants.

Performance of POCD vs. DPN Diagnosis by NCS. The majority (43 of 45) of the participants with abnormal results according to the POCD showed amplitude levels below the cut-off (≤4 μV; alone or together with slow CV). Only 2 participants were classified as abnormal due to bilateral abnormal sural CV alone (35.0 m/s [right] and 36.5 m/s [left] for 1 participant, and 36.7 m/s [right] and 37.0 m/s [left] for the other).

The performance of the POCD (abnormal or normal) by mean values of amplitudes and CVs of up to 3 bilateral measures (unilateral measures were obtained in 21 participants [13%]) showed a sensitivity of 78%, a specificity of 89%, a PPV of 71%, and an NPV of 92% against NCS (Table 2A). Very similar results were seen for the first bilateral measures (Table 2B). In contrast, Table 2C and D shows performance was lower using only the first measure from either the right or left leg. Higher sensitivity was achieved when an amplitude cut-off of 6 μV was chosen (96%), but the specificity decreased (71%) compared with the cut-off of 4 μV (Table 3A). The best performance of the POCD against NCS was seen when the borderline subjects (amplitude > 4 μV and ≤6 μV) were disregarded (Table 3B).

Table 1. Characteristics of participants by DPN status

Characteristics	DPN^+ from NCS (*n* = 45)	DPN^- from NCS (*n* = 123)	*P*-value
Sex (male)	35 (77.8)	77 (62.6)	0.065
Age (years)	71.5 (67.2–75.9)	69.4 (64.9–74.6)	0.147
Diabetes duration (years)	12.5 (10.0–14.1)	11.6 (9.9–13.6)	0.292
HbA_{1c} (%)	7.1 (3.2)	6.7 (3.1)	0.035
HbA_{1c} (mmol/mol)	51 (46–61)	48 (44–54)	0.035
Height (cm)	175 (169–181)	169 (163–174)	<0.001
Weight (kg)	90.4 (83.0–105.2)	86.9 (74.5–97.9)	0.037
BMI (kg/m^2)	30.1 (27.8–34.9)	30.5 (26.5–33.5)	0.719
SBP (mm Hg)	143 (131–152)	137 (127–150)	0.393

Categorical data are expressed as frequency (%) and continuous data are expressed as median (interquartile range). DPN, diabetic polyneuropathy; NCS, nerve conduction studies; HbA_{1c}, glycated hemoglobin; BMI, body mass index; SBP, systolic blood pressure.

POCD vs. DPN Diagnosis by NCS Sum-Scores Using ROC Curves. In Figure 1, the performance of POCD sural nerve amplitude and CV to distinguish between DPN^+ and DPN^- participants is illustrated using ROC curves. The ROC curves show a good sensitivity and specificity for POCD amplitudes with AUCs of >0.8, whereas POCD sural nerve CVs show fair sensitivity and specificity with AUCs between 0.7 and 0.8.

Linear Correlation between POCD and Conventional Sural NCS. In Figure 2, the correlation between levels of amplitudes and CVs by POCD and NCS is illustrated by log-transformed levels for normal distribution of data. There was a strong statistically significant correlation between levels of amplitude by the POCD and conventional sural NCS on the right and the left leg. Similarly, CVs by the POCD correlated significantly with CVs of conventional sural NCS both on the right and left leg; however, the correlations for CV were moderate and less significant than amplitudes.

Agreement between Levels of Amplitude and CV Measured by POCD and NCS. Levels of agreement between amplitudes and CVs measured by the 2 methods are depicted in Figure 3. A small, systematic difference between levels of both amplitudes and CVs can be seen (median difference in amplitude of −1.0 μV [25th–75th percentile: −3.6 to 1.1] and −0.6 μV [25th–75th percentile: −3.2 to 1.1]) for the right and left leg, respectively. The median difference in CV was 2.8 m/s (25th–75th percentile: −6.0 to 1.0) for the right leg and −3.4 m/s (25th–75th percentile: −7.5 to 0.1) for the left leg. The variation in measures of amplitude and CV did not appear to vary across the scale for the measurements. However, an underestimation of the amplitude, and particularly the CV, was seen with the POCD compared with conventional sural NCS. There was also a rather large variation in amplitude measurements between the 2 methods (95% confidence interval [CI] around ± 100%), with this being smaller for CVs (95% CI around ± 25%).

DISCUSSION

In this study we found a high concordance between the POCD and NCS measurements. Concurrently, sural nerve amplitudes and CVs assessed by the POCD

Table 2. Performance of POCD against nerve conduction studies (NCS) for diagnosing diabetic polyneuropathy (DPN)

(A) POCD using mean of up to 3 bilateral measures

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	35	14	49
	Normal	10	109	119
	Total	45	123	168

Sensitivity: 78% (95% CI 63–89%); specificity: 89% (95% CI 82–94); PPV: 71% (95% CI 57–83%); NPV: 92% (95% CI 85–96%).

(B) POCD using only first measures bilaterally

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	37	18	55
	Normal	8	105	113
	Total	45	123	168

Sensitivity: 82% (95% CI 68–92%); specificity: 85% (95% CI 78–91%); PPV: 67% (95% CI 53–79%); NPV: 93% (95% CI 87–97%).

(C) POCD using only first measure on right leg

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	36	26	62
	Normal	6	91	97
	Total	42	117	159

Sensitivity: 86% (95% CI 72–95%); specificity: 78% (95% CI 69–85%); PPV: 58% (95% CI 45–71%); NPV: 94% (95% CI 87–98%).

(D) POCD using only first measure on left leg

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	36	32	68
	Normal	5	83	88
	Total	41	115	156

Sensitivity: 88% (95% CI:74–96%); specificity: 72% (95% CI 63–80%); PPV 53% (95% CI: 40–65%); NPV 94% (95% CI 87–98%).

Performance of the point-of-care device (POCD) vs. NCS by: (A) mean values of up to 3 measures bilaterally; (B) the first measure on both legs; (C) only the first measure on the right leg; and (D) only the first measure on the left leg by calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Table 3. The performance of POCD against nerve conduction studies (NCS) for different cut-off levels for amplitude

(A) POCD with cut-off of 6 μV of amplitude

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	43	36	79
	Normal	2	87	89
	Total	45	123	168

Sensitivity: 96% (95% CI 85–100%); specificity: 71% (95% CI 62–79%); PPV: 54% (95% CI 43–66%); NPV: 98% (95% CI 92–100%).

(B) POCD when borderline results were disregarded

		DPN by NCS		
		DPN+	DPN−	Total
POCD	Abnormal	36	17	53
	Normal	2	87	89
	Total	38	104	142

Sensitivity: 95% (95% CI 82–99%); specificity: 84% (95% CI 75–90%); PPV: 68% (95% CI 54–80%); NPV: 98% (95% CI: 92–100%).

Performance of the point-of-care device (POCD) vs. NCS by: (A) using the cut-off of 6 μV of amplitude; and (B) disregarding the borderline results (amplitude > 4 μV and ≤6 μV) by calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

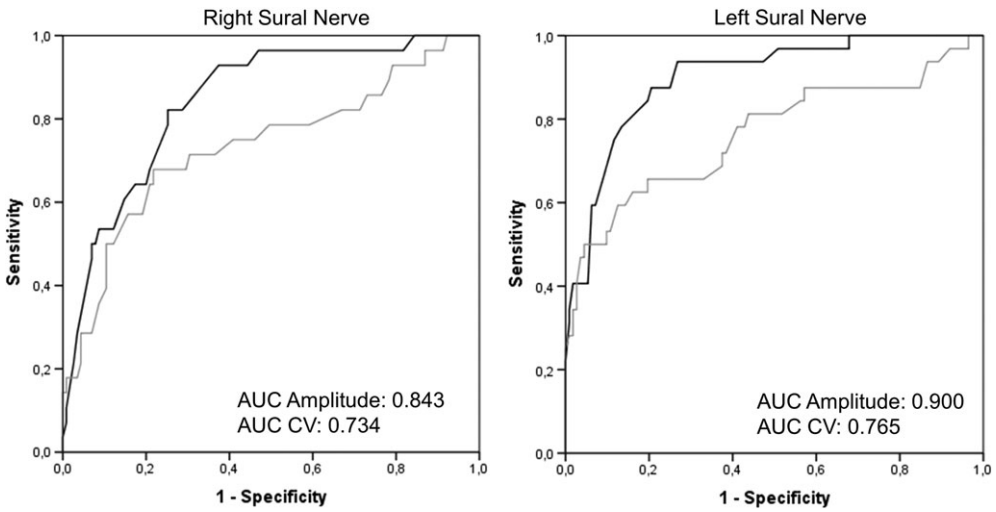

FIGURE 1. ROC curves illustrating area under the curve (AUC) of point-of-care device (POCD) amplitude (black curves) and conduction velocity (CV) (gray curves) to distinguish subjects with (DPN+) and without (DPN–) diabetic polyneuropaty (DPN).

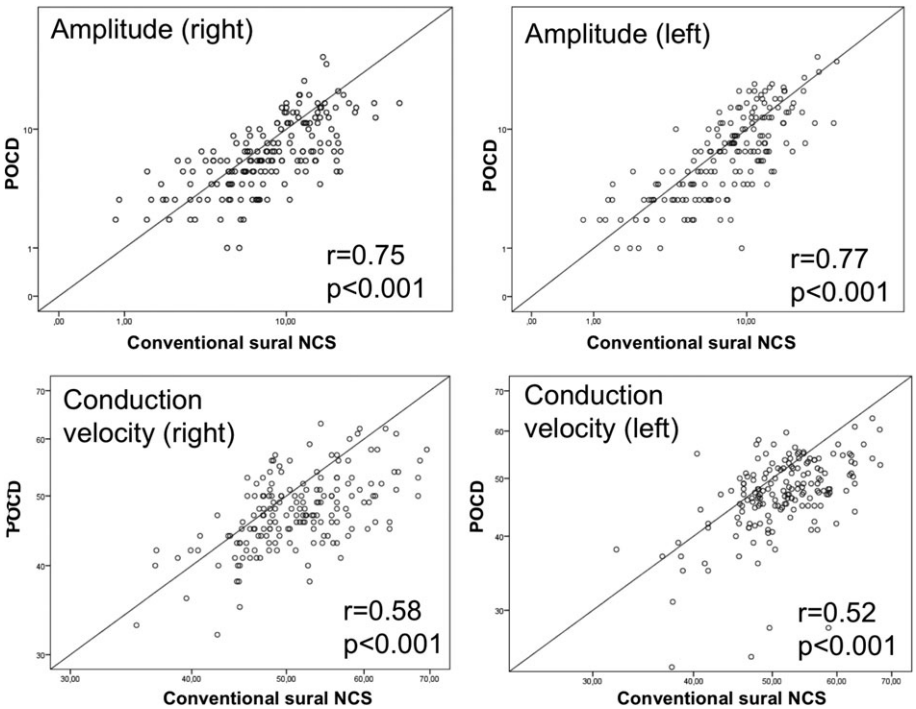

FIGURE 2. Correlations between sensory action potential amplitudes and conduction velocities of the sural nerve recorded by the point-of-care device (POCD) and conventional nerve conduction studies (NCS).

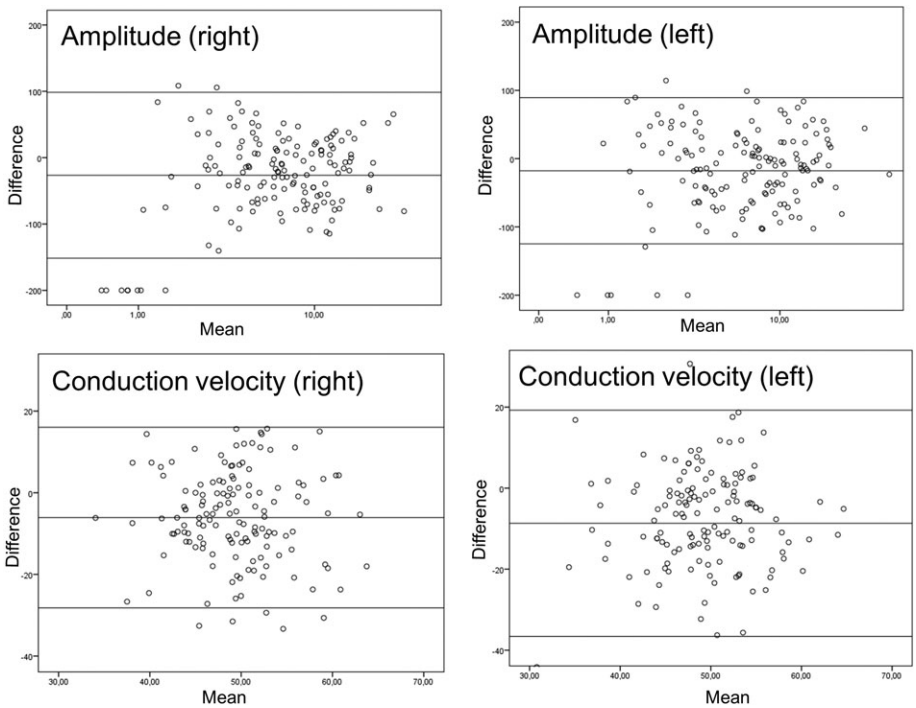

FIGURE 3. Agreement by Bland–Altman plots for point-of-care device (POCD) and conventional nerve conduction studies (NCS) of the sural nerve for amplitude and conduction velocity. The mean (POCD + conventional NCS / 2) values are shown on the x-axis and the percent difference [(POCD − conventional NCS / mean) × 100] values on the y-axis. The horizontal lines represent the 95% confidence intervals.

correlated significantly with NCS, but the agreement between measures was not very good and an underestimation of the amplitude and CV was seen with POCD compared with conventional NCS.

Previous studies have mainly investigated the utility of POCD in relation to symptoms and signs of neuropathy, monofilament testing, and 128-Hz tuning fork tests in subjects with diabetes[8,16–18] and

in patients with chemotherapy-induced neuropathy.[19] There have been 2 earlier studies comparing the POCD with conventional NCS in 72[6] and 44[7] subjects with diabetes. Perkins *et al.* found a sensitivity of 92% and a specificity of 82% for POCD amplitude compared with NCS-confirmed neuropathy. CV was not evaluated in their study and examinations were done unilaterally.[6] Lee *et al.* found a sensitivity of 95% and specificity of 71% for POCD amplitude or CV compared with conventional sural NCS using ROC curves.[7] An amplitude of < 6 μV for the POCD was defined as abnormal in both studies.[6,7] We found a similar sensitivity (96%) and specificity (71%) at a cut-off of 6 μV, whereas a cut-off of 4 μV lowered the sensitivity (78%) but increased the specificity (89%). Accordingly, PPV increased from 54% to 71%, whereas NPV decreased from 98% to 92% by lowering the cut-off from 6 μV to 4 μV. Performing the POCD examination once or up 3 times did not remarkably change the sensitivity or specificity. This suggests that more than 1 measurement does not improve accuracy.

We showed that examining 1 leg was insufficient and lowered both the specificity and PPV of the performance of the POCD against NCS. This may be explained by technical sources of error in abnormal measurements or concurrent diseases affecting nerve fibers unilaterally. Our results suggest that POCD studies should be performed on both legs.

The overall sensitivity was high and PPV was low for the POCD compared with NCS and we conclude that the device is best for ruling out DPN, whereas persons with abnormal results should be referred to conventional NCS. We also attempted to identify cut-off values of amplitudes to distinguish the subjects with and without neuropathy with best possible certainty. We believe describing a gray zone and prioritizing these subjects with diabetes for referral for conventional NCS could be of great clinical importance. When we excluded the 26 subjects with diabetes in the gray zone of 4–6 μV of amplitude, we showed the best performance of the POCD, with a sensitivity of 95%, a specificity of 84%, a PPV of 68%, and an NPV of 98%.

The use of CV slowing in isolation is not a generally accepted definition of neuropathy. However, there were only 2 individuals with decreased CV as the only abnormality, and we believe this had a minimal impact on our results. We found a better discrimination for DPN by POCD amplitude than POCD CV using ROC curves. Similarly, we found significant correlations between POCD and NCS measurements, with the correlation better for amplitude than for CV. However, there was an underestimation with the POCD, which was more pronounced for CV. The underestimation of amplitude can be explained by orthodromic recordings by the POCD vs. antidromic recordings by NCS. This underestimation and the less significant correlation of CV may have been due to temperature differences. The 2 measurements were done on the same day in different settings while the skin temperature was kept at >32°C for NCS; however, the POCD has a temperature correction algorithm, which will not necessarily yield similar results as NCS, because the POCD corrects the temperature only between 23° and 28°C and there is no temperature correction between 28° and 32°C. In contrast to our findings, Lee *et al.*[7] showed an overestimation of CV by POCD, which may depend on how high the temperature was kept during NCS in the study. Perkins *et al.*[6] found an underestimation of the amplitude, similar to our results. In spite of significant correlations between the POCD and conventional sural NCS, we found a considerable variance in Bland–Altman plots, particularly for amplitude (95% CI around ± 100%). Our results suggest that POCD performance was better when all NCS were taken into account rather than agreement with solely sural NCS. This may be due to the low sensitivity of conventional sural NCS compared with examination of other nerves and parameters, such as examination of the sural nerve with the near-nerve needle technique[20,21] or F-wave studies.[22]

In spite of the feasibility of the POCD, it has some limitations. The device is dependent on the presence of an accessible sural nerve. The anatomical variations of the sural nerve[23] may result in false positive results in patients who have absent responses or low-amplitude SNAPs on conventional NCS, because the device is not moved, as one would do during conventional NCS. The extremities are not warmed during POCD measurements and the device corrects the CV but not the amplitude for skin temperature. This raises the possibility that, in cool limbs, the amplitude will be falsely elevated with the POCD, and may decrease the sensitivity. Another limitation of the POCD is that the lowest amplitude reading is 1.5 μV. Below this value, the response is classified as zero.

We explored in this study the optimal procedure for the POCD and which diabetic patients should first be referred for NCS after screening. We found that 1 recording in both legs was the optimal procedure for measuring DPN in our cohort, whereas up to 3 measures bilaterally did not improve the performance significantly. Our results suggest that subjects with diabetes who have borderline values of amplitude should be referred for NCS. In addition, abnormal results require further referral for conventional NCS for a definitive evaluation, whereas normal POCD results suggest an absence of DPN with more certainty.

In conclusion, the results of this study suggest that the POCD is sufficiently accurate for potential use in clinics and for research purposes. Using the device may provide rapid and inexpensive screening for DPN, thereby reducing the need for referral to a specialized

clinical neurophysiology laboratory. The POCD may also be useful in large clinical trials as a rapid and quantitative measure of peripheral nerve function.

Ethical Publication Statement: We (the authors) confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Pastore C, Izura V, Geijo-Barrientos E, Dominguez JR. A comparison of electrophysiological tests for the early diagnosis of diabetic neuropathy. Muscle Nerve 1999;22:1667–1673
2. Tankisi H, Pugdahl K, Fuglsang-Frederiksen A, Johnsen B, de Carvalho M, Fawcett PR, *et al.* Pathophysiology inferred from electrodiagnostic nerve tests and classification of polyneuropathies. Suggested guidelines. Clin Neurophysiol 2005;116:1571–1580.
3. Weisman A, Bril V, Ngo M, Lovblom LE, Halpern EM, Orszag A, *et al.* Identification and prediction of diabetic sensorimotor polyneuropathy using individual and simple combinations of nerve conduction study parameters. PLoS One 2013;8:e58783.
4. O'Brien T, Karem J. An initial evaluation of a proof-of-concept 128-Hz electronic tuning fork in the detection of peripheral neuropathy. J Am Podiatr Med Assoc 2014;104:134–140.
5. Arshad AR, Alvi KY. Diagnostic accuracy of clinical methods for detection of diabetic sensory neuropathy. J Coll Phys Surg Pak 2016;26: 374–379.
6. Perkins BA, Grewal J, Ng E, Ngo M, Bril V. Validation of a novel point-of-care nerve conduction device for the detection of diabetic sensorimotor polyneuropathy. Diabetes Care 2006;29:2023–2027.
7. Lee JA, Halpern EM, Lovblom LE, Yeung E, Bril V, Perkins BA. Reliability and validity of a point-of-care sural nerve conduction device for identification of diabetic neuropathy. PLoS One 2014;9:e86515.
8. Hamasaki H, Hamasaki Y. Diabetic neuropathy evaluated by a novel device: sural nerve conduction is associated with glycemic control and ankle-brachial pressure index in Japanese patients with diabetes. Front Endocrinol (Lausanne) 2017;8:203.
9. Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G, *et al.* The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. Int J Obes Relat Metab Disord 2000;24(suppl 3):S6–11.
10. Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbaek A, *et al.* Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011;378:156–167.
11. Sandbaek A, Griffin SJ, Sharp SJ, Simmons RK, Borch-Johnsen K, Rutten GE, *et al.* Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe Study. Diabetes Care 2014;37:2015–2023.
12. Andersen ST, Witte DR, Dalsgaard EM, Andersen H, Nawroth P, Fleming T, *et al.* Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. Diabetes Care 2018;41:1068–1075.
13. Andersen ST, Witte DR, Andersen H, Bjerg L, Bruun NH, Jorgensen ME, *et al.* Risk-factor trajectories preceding diabetic polyneuropathy: ADDITION-Denmark. Diabetes Care 2018;41:1955–1962.
14. Falck B, Stålberg E, Bischoff C. Sensory nerve conduction studies with surface electrodes. Methods Clin Neurophysiol 1994;5:1–20.
15. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, *et al.* Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011;27: 620–628.
16. Sharma S, Vas PR, Rayman G. Assessment of diabetic neuropathy using a point-of-care nerve conduction device shows significant associations with the LDIFLARE method and clinical neuropathy scoring. J Diabetes Sci Technol 2015;9:123–131.
17. Hirayasu K, Sasaki H, Kishimoto S, Kurisu S, Noda K, Ogawa K, *et al.* Difference in normal limit values of nerve conduction parameters between Westerners and Japanese people might need to be considered when diagnosing diabetic polyneuropathy using a Point-of-Care Sural Nerve Conduction Device (NC-stat(R)/DPNCheck). J Diabetes Investig 2018;9:1173–1181.
18. Brown JJ, Pribesh SL, Baskette KG, Vinik AI, Colberg SR. A comparison of screening tools for the early detection of peripheral neuropathy in adults with and without type 2 diabetes. J Diabetes Res 2017;2017: 1467213.
19. Matsuoka A, Mitsuma A, Maeda O, Kajiyama H, Kiyoi H, Kodera Y, *et al.* Quantitative assessment of chemotherapy-induced peripheral neurotoxicity using a point-of-care nerve conduction device. Cancer Sci 2016; 107:1453–1457.
20. Kural MA, Pugdahl K, Fuglsang-Frederiksen A, Andersen H, Tankisi H. Near-nerve needle technique versus surface electrode recordings in electrodiagnosis of diabetic polyneuropathy. J Clin Neurophysiol 2016; 33:346–349.
21. Kural MA, Karlsson P, Pugdahl K, Isak B, Fuglsang-Frederiksen A, Tankisi H. Diagnostic utility of distal nerve conduction studies and sural near-nerve needle recording in polyneuropathy. Clin Neurophysiol 2017;128:1590–1595.
22. Andersen H, Stalberg E, Falck B. F-wave latency, the most sensitive nerve conduction parameter in patients with diabetes mellitus. Muscle Nerve 1997;20:1296–1302.
23. Tankisi H, Pugdahl K, Otto M, Fuglsang-Frederiksen A. Misinterpretation of sural nerve conduction studies due to anatomical variation. Clin Neurophysiol 2014;125:2115–2121.