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The assessment of clinical distal symmetric polyneuropathy in type 1 diabetes: A comparison of methodologies from the Pittsburgh Epidemiology of Diabetes Complications Cohort

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ABSTRACT

Distal symmetrical polyneuropathy (DSP) is the most common type of diabetic neuropathy, but often difficult to diagnose reliably. We evaluated the cross-sectional association between three point-of-care devices, Vibratron II, NC-stat®, and Neurometer®, and two clinical protocols, MNSI and monofilament, in identifying those with DSP, and/or amputation/ulcer/neuropathic pain (AUP), the two outcomes of major concern. This report presents data from 195 type 1 diabetic participants of the Epidemiology of Diabetes Complications (EDC) Study attending the 18-year examination (2004–2006). Participants with physician-diagnosed DSP, AUP or who were abnormal on the NC-stat, and the Vibratron II, MNSI, and monofilament were older ($p < 0.05$) and had a longer duration of diabetes ($p < 0.05$). There was no difference by sex for DSP, AUP, or any testing modality, with the exception of NCstat (motor). The Vibratron II and MNSI showed the highest sensitivity for DSP (>87%) and AUP (>80%), whereas the monofilament had the highest specificity (98% DSP, 94% AUP) and positive predictive value (89% DSP, 47% AUP), but lowest sensitivity (20% DSP, 30% AUP). The MNSI also had the highest negative predictive value (83%) and Youden's Index (37%) and currently presents the single best combination of sensitivity and specificity of DSP in type 1 diabetes.

1. Introduction

Neuropathy, a common complication of type 1 and type 2 diabetes mellitus, may affect 28–70% of patients, depending upon the population characteristics, diabetes duration and diagnostic methodology used [1–6]. Although all types of peripheral nerves can be involved, it is usually sensory dominant with eventual involvement of motor nerve fibers [7]. Distal symmetrical polyneuropathy (DSP), which predisposes patients to variable pain, sensory disturbance, motor dysfunction, ulcers, and gangrene, is the most common type of diabetic neuropathy [8–10]. DSP, however, is difficult to diagnose because it is frequently subtle and requires clinical judgment and/or expensive and subsequent unpleasant testing modalities like nerve conduction. Patients may also be asymptomatic for years and diagnosis may only be apparent with a complication like painless foot ulcer. As over 80% of amputations follow a foot ulcer or injury and the total annual cost of DSP and its complications is estimated to be between $4.6 and $13.7 billion [11], early reliable identification of individuals at risk is a public health issue as well as a clinical concern [8].

In the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), a 20 year prospective cohort of childhood onset type 1 diabetes, we have reported strong relationships of DSP with foot ulcers/amputation [12], coronary artery disease [13], and coronary artery calcification [14]. DSP risk factors comprised hypertension, diabetes duration, and glycosylated hemoglobin [15]. Other studies have reported similar findings with neuropathy [16–19].

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Unfortunately, there is no diagnostic gold standard for DSP and the use of multiple testing modalities is recommended [20]. Current standards of medical care by the American Diabetes Association recommend that all patients with diabetes should be screened annually for DSP using a variety of tests such as pinprick, sensation, vibration perception (using a 128 Hz tuning fork), 10 g (Semmes–Weinstein) monofilament pressure sensation at the distal halluces, and ankle reflexes [8]. No specific protocol is given, however, and a number of newer point-of-care instruments, Neurometer R-CPT (Neurotron, Inc.) and NC-stat (NEUROMetrix, Inc.), are now also available, in addition to older devices like the Vibratron II assessment of vibratory sensation, and clinical protocols like the Michigan Neuropathy Screening Index (MNSI), and monofilament. These instruments and protocols might enable more widespread technician screening and possibly earlier diagnosis, than would be possible using formal physician exams or nerve conduction studies.

In this cross-sectional analysis, we thus evaluated the Vibratron II, NC-stat (NEUROMetrix, Inc.) and Neurometer R-CPT (Neurotron, Inc.) devices, and the MNSI and monofilament protocols as indicators of clinically diagnosed DSP. The common outcome or ''Gold Standard'' to which they were all thus compared was a standard clinical exam protocol replicating use in general clinical practice. We also studied the other device/protocol associations against the NC-stat as an alternative (nerve conduction-based) Gold Standard. Finally, we examined the associations of these measures with the major clinical outcomes of neuropathy that are of concern to the patient and healthcare provider, i.e., presence of ulcer/amputation and/or neuropathic pain.

2. Method

2.1. Population

The subjects were participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a prospective study of risk factors for complications of childhood onset (<17 years of age at diagnosis) type 1 diabetes, diagnosed (or seen within one year of diagnosis) at Children's Hospital of Pittsburgh between 1950 and 1980. This population has been shown to be epidemiologically representative of the Allegheny County type 1 diabetes population [21]. The EDC Study first examined participants between 1986 and 1988 and then biennially thereafter for 10 years and again at 18 years. This report presents cross-sectional data from 195 participants attending the 18 year examination (2004–2006) with available clinical exam data, Vibratron II testing, and NC-stat, which was introduced partway into the clinical examination period. As there was no assessment of neuropathy in the finger with the NCstat, this analysis is confined to the foot and especially the hallux. In a subgroup of 141 participants, the Neurometer was similarly evaluated.

2.2. Vibratory sensory thresholds: Vibratron II (Physitemp Instruments, Clifton, NJ)

Sensory thresholds were measured on the palmar aspect of the distal phalanx of the index finger and plantar aspect of the great toe on the dominant side of the body. The protocol uses the two alternative forced-choice methods, where the participant was required to indicate which of the two posts was vibrating as previously described [22]. The vibratory thresholds were examined as follows: the unadjusted for age raw score (continuous variable), and a categorical age-adjusted score. The criteria for the abnormal age-specific vibratory thresholds are >2.39, >2.56, and >2.89 vibration units for ages ≤35, 36–50, and >50 years, respectively [23].

2.2.1. NC-stat (NEUROMetrix, Inc.)

The NC-stat is a point-of-care device designed to perform standard noninvasive nerve conduction studies by non-technical personnel. The NC-stat device does not represent a new diagnostic technology but rather a further evolution of existing nerve conduction studies (NCS) methods. The testing was focused on the compound muscle action potential (CMAP) for the peroneal (motor F wave latency) nerve and the sural nerve amplitude potential (SNAP) for the sensory nerve at the region of the foot and ankle. Using a special alcohol and pumice prep pad, the foot was scrubbed and allowed to dry. For the tibial (sural) test, the electrode/biosensor was placed on the subject's ankle and the biosensor connected to the monitor, while for the peroneal (motor) the hallucis longus tendon was identified by having the patient flex his/her toes upward. The location was marked, the electrode/biosensor applied, and then the biosensor electrode was connected to the monitor. The NC-stat is equipped with a remote-on-call system which transmits the data from the monitor to the central reading center where a report was generated and sent to the clinic by fax. The testing took approximately 15 min. The sensory raw score was not normally distributed, despite log transformation, and thus analysed two ways: ≥6 μV or <6 μV, based on conventional criteria (SNAP), and any vs. no response (NCstat sensory). The latter stratification was based upon the limitations of the NCstat's sensory nerve amplitude which lacks signal detection for extremely low levels of sural nerve sensory amplitude and zeros all signals <2.1 μV. The motor data were dichotomized as normal or abnormal (CMAP).

2.2.2. Neurometer R-CPT (Neurotron, Inc.)

In a subgroup of participants (n = 141), the Neurometer R-CPT (Neurotron, Inc.), which was introduced later, was also available. The Neurometer is a portable point of care device which stimulates peripheral sensory nerve fibers in the great toe on the right foot at three frequencies, 2000 Hz (A_β fibers), 250 Hz (A_δ fibers), and 5 Hz (C fibers). Each frequency is repeated several times to ensure accuracy and reproducibility. The average time needed to complete the three tests was less than 5 minutes. The Neurometer reports values as the normal range (R-CPT Level, 6–13), hyperesthesia (R-CPT Level, 1–5), and hypoesthesia (R-CPT Level, 14–25). Due to the nonlinear scoring, analyses were performed having categorized participants as being normal, hyperesthesia, or hypoesthesia.

2.2.3. MNSI examination

MNSI examination is a structured clinical assessment of the feet to identify deformities, dry skin, calluses, infection, fissure, or ulcers (foot appearance), and evaluation of ankle reflexes and vibration sensation in the great toe. The foot

appearance examination was conducted by a trained study technician and the evaluation of the ankle reflexes and vibration sensation were conducted by the study physician. A score of ≥2 on the MNSI examination was considered a positive result [24].

2.2.4. *Monofilament*

The 10 g Semmes–Weinstein monofilament (Sensory Testing Systems®, Baton Rouge, LA) is a test of protective sensation/pressure on the dorsum of the great toe. This was done ten times for each foot with the subject's eyes closed. The participant was instructed to answer ''yes or no'' in response to filament pressure. For the purposes of the current analyses, the monofilament variable was dichotomized as follows: 8–10 correct responses–normal; 0–7 correct responses–abnormal.

2.3. *Outcome variables*

2.3.1. *Distal symmetric polyneuropathy (DSP)*

Distal symmetric polyneuropathy was determined by a study-trained physician using the Diabetes Control and Complications Trial clinical examination protocol [25]. A standard clinical history was taken and addressed any concurrent disease processes that could cause neuropathy, exposure to known neurotoxins, and a family history of neuromuscular disorders. Participants were questioned about symptoms and positive responses were recorded, e.g., numbness, dysesthesias, and/or paresthesias, hypersensitivity to touch, burning and/or aching, and stabbing pain in the hands or feet. A standard neurological examination follows and includes evaluation of reflex activity, pain (pinprick), vibration (tuning fork, 128 Hz), sensation, and position. DSP was defined as the presence of two or more of the following: symptoms, sensory and/or motor signs, and/or absent (or present only with reinforcement) tendon reflexes.

2.3.2. *Amputation/ulcer/neuropathic pain (AUP)*

Amputation/ulcer was determined by the study-trained physician. The physician performed a bilateral examination of the lower extremities and rated each leg as follows: normal, no ulcer or amputation, ischemic, ulcer, gangrene, amputation, infection, necrotic diabetic, or other. In addition, ulcers were graded individually as follows: normal, ischemic neurotropic, venous stasis, present-type uncertain. If a study participant did not return to the clinic for an 18 year physician examination, amputation status was determined from the survey data remitted. Neuropathic pain was defined as a positive response to the question concerning burning, aching, or stabbing pain in the absence of a more likely cause. The clinical outcome thus studied was the combination of amputation and/or ulcer and/or neuropathic pain in the hands, feet, or both hands and feet.

2.4. *Statistical analysis*

The SPSS/PC statistical software (SPSS, Chicago, IL) was used for all cross-sectional analyses. The Kolmogorov–Smirnov test was used to assess normality of the distribution. All variables that violated the assumption of normality were log-transformed. Group differences in categorical variables were tested with X^2 tests, while the student's *t*-test and ANOVA, with Bonferroni's correction for multiple comparisons, were used for the continuous variables. The sensitivity, specificity, and Youden's index were calculated. Similarly, the Neurometer was evaluated in the smaller subgroup with these measures.

HbA1c and height were sex-adjusted.

3. Results

There were no differences in age, sex, or duration of diabetes between the 195 participants with complete data and participants with incomplete data (data not shown). The main demographic characteristics of participants, stratified by the various neuropathy classifications, are listed in Table 1. Participants with physician-diagnosed DSP, AUP or who were abnormal on the NC-stat, and the Vibratron II, MNSI, and monofilament were older ($p < 0.05$) and had a longer duration of diabetes ($p < 0.05$). There was no difference by sex, with the exception of the NCstat (sensory) ($p = 0.07$) and NCstat (motor) ($p < 0.01$), where males were more likely to be cases. HbA1c was higher in participants diagnosed with DSP, AUP, and with abnormal NC-stat (all categories) and MNSI ($p < 0.05$) results. Moreover, HbA1c was marginally higher in participants testing positive for the monofilament ($p = 0.07$). There were no differences in age, duration of diabetes, sex, height, or HbA1c within each classification or between each frequency of the Neurometer, with the exception of the 5 Hz frequency where participants classified with hypoesthesia were older than participants classified as normal and the 250 Hz frequency where participants diagnosed with hypoesthesia were older than participants diagnosed with hyperesthesia, although both differences were only borderline significant ($p < 0.07$, $p < 0.09$, respectively).

Table 2 reports the screening characteristics for the neuropathy measures compared to the DSP outcome. Age-adjusted Vibratron II and MNSI showed the highest sensitivity (>87%). However, the Vibratron also demonstrated the lowest specificity (0.26). The monofilament had not only the highest specificity (0.98) and PPV (0.89), but also the lowest sensitivity (0.20). The MNSI had the highest NPV (0.83) and Youden's index (0.37), suggesting the better overall association with the clinical examination.

Table 3 reports the screening characteristics for the neuropathy measures compared to the AUP outcome. Again, the age-adjusted Vibratron II showed the highest sensitivity (0.90) and lowest specificity (0.20). The NC-Stat (SNAP), and MNSI showed a moderate sensitivity (≥77%) while, monofilament still maintained the highest specificity (0.94). The Positive Predictive Values (PPVs) were consistently lower for the AUP outcome than the clinical DSP outcome. The monofilament again had the highest PPV (though it was approximately half its PPV for DSP) and the highest Youden's index (0.24). Analyses were repeated separating out the amputation and ulcer (Table 3a) from the neuropathic pain (Table 3b). Similar patterns were seen for neuropathic pain but the sensitivity of all testing modalities is higher for amputation and/or ulcer. This is especially true for the monofilament where the sensitivity for amputation and/or ulcer is 0.62.

Table 1 – Demographic characteristics by neuropathy assessment at 18 years of follow up.

$n = 195$	Age (years)	Duration (years)	Sex (%F)	Height (cm)‡	HbA1c (%)‡
Distal symmetrical polyneuropathy					
Noncase	41.4 ± 6.5	33.6 ± 5.2	48	167.9 ± 9.1	7.3 ± 1.4
Case	46.2 ± 7.2†	38.3 ± 7.2†	53	167.5 ± 9.7	7.7 ± 1.3*
Amputation/ulcer/pain					
Noncase	43.2 ± 7.0	35.1 ± 6.3	50	167.7 ± 9.7	7.4 ± 1.3
Case	46.6 ± 8.1*	38.8 ± 7.2†	53	167.8 ± 9.3	7.9 ± 1.4*
NC-stat®					
SNAP noncase	39.9 ± 6.3	32.8 ± 5.5	51	167.6 ± 9.7	7.1 ± 1.1
Case	45.8 ± 6.9†	37.2 ± 6.6†	50	167.8 ± 9.6	7.7 ± 1.4†
Sensory†† noncase	42.1 ± 6.8	34.4 ± 5.7	55	167.5 ± 9.8	7.3 ± 1.2
Case	46.6 ± 7.3†	37.9 ± 7.3†	44	168.2 ± 9.1	7.8 ± 1.5*
Motor noncase	42.4 ± 7.2	34.6 ± 6.2	60	167.5 ± 9.7	7.3 ± 1.2
Case	46.3 ± 6.9†	37.6 ± 6.9†	32†	168.2 ± 8.8	7.9 ± 1.5†
Vibratron II					
Noncase	39.9 ± 6.6	33.0 ± 5.5	64	166.6 ± 9.0	7.4 ± 1.3
Case	44.5 ± 7.2†	36.2 ± 6.6†	48	167.9 ± 9.7	7.5 ± 1.3
MNSI					
Noncase	40.5 ± 6.5	33.1 ± 5.2	51	166.9 ± 9.8	7.2 ± 1.1
Case	45.3 ± 7.2†	36.6 ± 6.8†	51	168.2 ± 9.5	7.6 ± 1.4*
Monofilament					
Noncase	43.1 ± 7.1	35.2 ± 6.3	51	167.5 ± 9.6	7.4 ± 1.3
Case	48.7 ± 6.3†	39.8 ± 7.2†	47	169.6 ± 9.5	8.0 ± 1.2
$n = 141$					
Neurometer					
2000 Hz noncase	42.3 ± 7.2	34.5 ± 6.6	49	167.1 ± 9.3	7.3 ± 1.1
Hyperesthesia	37.7 ± 8.3	30.7 ± 2.3	67	172.0 ± 7.5	7.9 ± 1.2
Hypoesthesia	44.5 ± 6.9	36.1 ± 6.4	46	167.9± 9.4	7.6 ± 1.5
250 Hz noncase	43.9 ± 8.8	35.6 ± 6.9	42	167.3 ± 8.9	7.3 ± .95
Hyperesthesia	38.5 ± 9.4	32.9 ± 5.8	56	169.4 ± 10.1	6.7 ± 1.1
Hypoesthesia	43.9 ± 6.5	35.6 ± 6.4	49	167.7 ± 9.5	7.7 ± 1.5
5 Hz noncase	42.6 ± 6.5	34.5 ± 6.1	52	166.6 ± 9.7	7.6 ± 1.4
Hyperesthesia	41.7 ± 10.1	35.5 ± 8.3	42	170.0 ± 6.9	7.2 ± 1.4
Hypoesthesia	45.6± 6.9¶¶	36.8 ± 6.4	42	168.8 ± 8.9	7.4 ± 1.2
2000 Hz noncase‡‡	42.3± 7.2	34.5± 6.6	49	167.1 ± 9.3	7.3 ± 1.1
case	44.3 ± 7.0	35.9 ± 6.4	47	168.1 ± 9.3	7.6 ‡ ± 1.5
250 Hz noncase‡‡	43.9 ± 7.8	35.6 ± 6.9	42	167.3 ± 8.9	7.3 ± 0.95
Case	43.5 ± 6.9	35.4 ± 6.3	49	167.8 ± 9.5	7.6 ± 1.5
5 Hz noncase‡‡	42.6 ± 6.5	34.5 ± 6.1	52	166.6 ± 9.7	7.6 ± 1.4
Case	44.8 ± 7.7	36.6 ± 6.7	42	169.1 ± 8.5*	7.3 ± 1.2

Data are means ± SD.
* $p < 0.05$.
† $p < 0.01$.
‡ Sex adjusted.
†† NCSTAT sensory (any vs. none).
‡‡ Hyperesthesia + hypoesthesia.
¶¶ $p < 0.07$ between normal and hypoesthesia.

The screening characteristics for the neuropathy measures, including DSP, are compared to NC-stat (SNAP) in Table 4. The Vibratron II has the highest sensitivity for the NC-stat (0.88), while the monofilament has the highest specificity (1.00). Finally, DSP has just moderate sensitivity (0.54) for the NC-stat (SNAP), but reasonable specificity (0.74).

The Neurometer (normal vs. (hyperesthesia + hypoesthesia)) was compared to the DSP and AUP outcomes in Table 5. The

Table 2 – Screening characteristics of NcStat® and Vibratron II devices, MNSI, and monofilament for the detection of clinically diagnosed distal symmetrical polyneuropathy.

$n = 195$	Sensitivity	Specificity	PPV	NPV	Youden
NC-stat® SNAP	0.79	0.48	0.54	0.74	0.27
Sensory	0.53	0.77	0.65	0.68	0.31
Motor	0.46	0.76	0.61	0.64	0.22
Vibratron-age adjusted	0.91	0.26	0.49	0.78	0.16
MNSI	0.87	0.49	0.58	0.83	0.37
Monofilament	0.20	0.98	0.89	0.61	0.18

Table 3 – Screening characteristics of NcStat® and Vibratron II devices, MNSI, and monofilament for the detection of amputation/ulcer/neuropathic pain.

$n = 195$	Sensitivity	Specificity	PPV	NPV	Youden
NC-stat® SNAP	0.77	0.38	0.18	0.90	0.15
Sensory	0.53	0.67	0.22	0.89	0.20
Motor	0.53	0.70	0.24	0.89	0.23
Vibratron-age adjusted	0.90	0.20	0.17	0.92	0.10
MNSI	0.80	0.36	0.18	0.91	0.16
Monofilament	0.30	0.94	0.47	0.88	0.24

Table 3a – Screening characteristics of NcStat® and Vibratron II devices, MNSI, and monofilament for the detection of amputation and/or ulcer at cycle 10.

$n = 195$	Sensitivity	Specificity	PPV	NPV	Youden
NC-stat® SNAP	0.87	0.37	0.06	0.98	0.24
Sensory	0.75	0.65	0.08	0.98	0.40
Motor	0.75	0.68	0.09	0.98	0.43
Vibratron-age adjusted	1.0	0.19	0.05	1.0	0.19
MNSI	1.0	0.35	0.06	1.0	0.35
Monofilament	0.62	0.92	0.26	0.98	0.54

Table 3b – Screening characteristics of NcStat® and Vibratron II Devices, MNSI, and monofilament for the detection of neuropathic pain[a] at cycle 10.

$n = 195$	Sensitivity	Specificity	PPV	NPV	Youden
NC-stat® SNAP	0.79	0.41	0.30	0.86	0.20
Sensory	0.54	0.69	0.37	0.82	0.23
Motor	0.54	0.73	0.39	0.83	0.27
Vibratron-age adjusted	0.94	0.22	0.28	0.92	0.16
MNSI	0.81	0.38	0.30	0.86	0.19
Monofilament	0.25	0.95	0.63	0.79	0.20

[a] No DSP + DSP(no pain) vs. DSP(pain).

250 Hz frequency had the highest sensitivity (0.79, 0.79) and NPV (0.66, 0.87) but the lowest Youden's Index (0.11, 0.07) for the DSP and AUP outcomes, respectively. The 5 Hz frequency had not only the highest specificity (0.61, 0.57) and PPV (0.52, 0.20), but also the lowest sensitivity (0.51, 0.50) for DSP and AUP, respectively. The specificity and PPV values for each of the Neurometer frequencies were much lower for the AUP as compared to the DSP outcome. The Youden's Index was low for each frequency, suggesting very little association with either outcome.

Table 4 – Screening characteristics of the Vibratron II Device, MNSI, and monofilament for the detection of abnormal NC-stat® (SNAP).

$n = 195$	Sensitivity	Specificity	PPV	NPV	Youden
Vibratron-age adjusted	0.88	0.30	0.69	0.58	0.18
MNSI	0.80	0.57	0.77	0.61	0.37
MONOFILAMENT	0.15	1.00	1.00	0.40	0.15
DSP	0.54	0.74	0.79	0.48	0.29

Table 5 – Screening characteristics of the Neurometer®[a] for the detection of clinically diagnosed distal symmetrical polyneuropathy and amputation/ulcer/neuropathic pain.

$n = 141$	Sensitivity	Specificity	PPV	NPV	Youden
Clinically diagnosed distal symmetrical polyneuropathy					
2000 Hz	0.71	0.42	0.50	0.65	0.13
250 Hz	0.79	0.32	0.48	0.66	0.11
5 Hz	0.51	0.61	0.52	0.61	0.12
Amputation/ulcer/neuropathic pain					
2000 Hz	0.71	0.38	0.19	0.86	0.09
250 Hz	0.79	0.28	0.18	0.87	0.07
5 Hz	0.50	0.57	0.20	0.85	0.07

[a] Normal vs. (hyperesthesia + hypoesthesia).

4. Discussion

These results provide confirmation of the utility of the Vibratron II and especially the MNSI exam in the detection of neuropathy in longstanding type 1 diabetes. The relatively more limited association between the NC-stat and clinical DSP raises the issue that they may be focusing on different fibers. The sensitivity and specificity of the 10 g monofilament is consistent with other studies, as is its better sensitivity for amputation/ulcer/neuropathic pain.

DSP is a common and diverse complication of type 1 diabetes that adversely impacts the quality of life. It is a condition that predisposes to clinical end points, such as foot ulceration and amputation [26], which are disastrous complications from an individual, social, and economic perspective. A recent study in France [27] demonstrated that neurological disease, in particular, was an important contributor to diabetic amputation, whatever the major pathway. Thus, the early diagnosis of diabetic neuropathy is essential to identify patients at risk for latent complications (especially ulcer and amputation).

Nerve conduction studies, which are considered by many to be the gold standard, are very accurate, objective, and sensitive to the study of progression and severity of neuropathy [28,29], but are also expensive and time-consuming. In addition, nerve conduction has limited availability, rendering it impractical as a population-based screening tool. This cross-sectional examination of a type 1 diabetes cohort provided the opportunity to examine the sensitivity, specificity, PPV, and NPV of four separate neuropathy assessment modalities to determine which, if any, were most closely associated with clinical detected DSP and/or presence of amputation/ulcer/neuropathic pain. Moreover, as the NC-stat is based upon the same underlying physiology as traditional nerve conduction, we further sought to examine the association of the other neuropathy measures (and DSP) with this test representing the ''Gold Standard''.

The choice of gold standards for assessing the point-of-care devices and shorten protocols is, of course, debatable. However, we believe both standards studied here are relevant. The clinical DSP provides for the use of these device protocols as a screening tool by non MD personnel to identify those at clinical risk. The alternative NC-stat provides information for those who believe identifying the underlying process, rather than the clinical manifestation, is important.

Our results show that the MNSI clinical exam and the Vibratron II were the most sensitive measures of clinical DSP (0.87, 0.91, respectively) and AUP (0.80, 0.90, respectively), but their specificity was poor for both complication outcomes. However, the NPV for both the MNSI and Vibratron II are acceptable for many applications being approximately 80%. The MNSI clinical exam is a validated instrument [30] that can be implemented for a very low cost. Non-physician personnel can be trained and certified to administer the exam, which suggest a wide-ranging application. The MNSI was successfully implemented in a global study [31], where it correlated significantly with reported history of neuropathy at both the study center and individual levels. As health care system performance, social distribution of wealth and purchasing power may play important roles in explaining the geographic variation of diabetes complications [32], the MNSI may be the screening tool of choice for neuropathy.

The age-adjusted Vibratron II proved to be a sensitive measure of DSP and AUP, but lacked the specificity of the NC-stat and monofilament. As a change in the ability to perceive vibratory stimuli is recognized as an early and reliable sign of dysfunction [33], it is likely the Vibratron II is detecting subclinical abnormalities and may be diagnosing an early stage of clinical disorder. This is the current focus for our longitudinal data in the Epidemiology Diabetes Complications Study (EDC).

The monofilament is too insensitive an instrument (0.20, DSP: 0.30, AUP) for use as a single screen, however, it has a high degree of specificity (0.98, DSP: 0.94, AUP) and PPV (0.89 DSP: 0.47 AUP) for both complication outcomes and thus may be very helpful where identification of only those with a high probability of disease (e.g., an intervention with major side effects) is critical. The monofilament has been shown to predict foot ulcers and amputations [34–36] in previous studies and thus is most useful in identifying those at risk of foot ulceration. This is consistent with current results wherein the sensitivity of the monofilament is much higher (0.62) for amputation and ulcer than for pain (0.25) (Tables 3a and 3b). In a recent multicenter trial [36], the combination of the Neuropathy Disability Score (NDS) and the monofilament could identify all but one of the 95 ulcerated feet. The monofilament is very simple, easy to perform, takes very little time, and is inexpensive, so it can be used almost anywhere in the world without any significant financial burden.

There were no gender differences noted between the different neuropathy testing modalities, with the exception of the NC-stat motor nerve testing (CMAP), where males were significantly more likely to test positive. Similar findings were seen in a recent study comparing neuropathy patterns in patients with diabetic complications [37]. The authors found that muscle weakness and atrophy, as well as unilateral or bilateral peroneal nerve unresponsiveness, were significantly different by gender and concluded that peroneal involvement was more common and severe in diabetic males.

The NC-stat, a novel point-of-care device, has previously been shown to have diagnostic accuracy [38,39] and has been purported to represent an accurate alternative to traditional NCS methods for detecting diabetic sensorimotor polyneuropathy. As the NC-stat is touted as a mainstream alternative to traditional NCS methods, we examined the sensitivity and specificity of the other neuropathy measures, as well as DSP and AUP, for the NC-stat outcome. The screening characteristics of the Vibratron, MNSI, and monofilament were generally similar for NC-stat as they were for DSP. However, DSP demonstrated only a sensitivity of 0.54 compared to NC-stat (SNAP), while NC-stat had a sensitivity of 0.79 for DSP. While this is consistent with NC-stat (SNAP) detecting participants with underlying disease some of whom have yet to detect symptoms, this does raise the issue as to whether nerve conduction abnormalities are always followed by significant clinical disease [33–40].

Previous NC-stat study populations have consisted of very few type 1 diabetes participants, which may account for the disparity of the results. An earlier study examining the effects

of age, sex, and type of diabetes on diabetic neuropathy reported that the relationship between nerve conduction measures and age, sex, and gender were similar for normal subjects and patients with type 2 diabetes, but not for those with type 1 diabetes. This finding, the authors suggested, represents a lack of homogeneity, with respect to neuropathy, in type 1 diabetes [41]. This difference in type 1 diabetes is supported by the data in this study, where the SNAP value of 3.29 μV had a comparable sensitivity (0.72) and greater specificity (0.67) for DSP than the established cut point of 6.0 μV for DSP. This is why our alternative category of 'any response' is helpful and perhaps preferable in type 1 diabetes. This observation, however, needs to be confirmed in further studies.

Neurometer data were not available on all participants and hence its analysis was limited and incomparable to the other neuropathy assessment tools in this study. Moreover, the sample size prohibited closer analysis of the respective Neurometer categories (normal, hyperesthesia, hypoesthesia) and their possible relationship to DSP. However, the 2000 Hz and 250 Hz frequencies for the Neurometer had a sensitivity and specificity for DSP and AUP that was similar to the NC-stat (SNAP), indicating possible detection of subclinical disease.

The exclusion of the upper extremities in this study may be considered a limitation of this analysis. However, DSP usually starts in the feet [33]. The cross-sectional nature of the analysis is also a limitation. We recognize that the subjects' exposure status at the time of this study may have little to do with their exposure status at the time the disease began and plan to repeat this analysis when follow up data are available. Our sample size is also a limitation of this analysis, as only 64% of the participants at the 18 year exam have complete data for this analysis (195/304) due to the late incorporation of the tests into the exam cycle.

In conclusion, although neuropathy devices such as NC-stat and Vibratron II, and to a lesser degree the Neurometer, are fairly sensitive measures, their reduced specificity for DSP diminishes their value as diagnostic tools in individuals with type 1 diabetes, and they do not perform well against NC-stat as a gold standard. Thus, the MNSI examination currently presents the single best combination of sensitivity and specificity of DSP in type 1 diabetes. Though this association may partially reflect the close association of DSP and MNSI features (reflexes, vibration, sensation), it is nonetheless clinically important. The monofilament, though it has low sensitivity, remains a very specific testing modality and has a useful role where this is an important consideration.

Conflict of interest

The authors declare that they have no conflict of interest.

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