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Original Article

PainVision™: a simple, rapid, and objective method with potential for screening diabetic peripheral neuropathy

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Abstract: Background and objective: Clinical methods for diabetic peripheral neuropathy (DPN) detection are not objective and reproducible. We therefore evaluated whether PainVision™, a new method developed to provide a quick, non-invasive and quantitative sensory function assessment, can be reliably used to screen DPN. Material and methods: A total of 49 patients with type 2 diabetes mellitus and peripheral neuropathy (DPN group) and 43 non-diabetic subjects (Non-DPN group) underwent clinical evaluation using a quantitative measurement device (PainVision) for perception and pain to determine current perception threshold (CPT); in addition, the Michigan diabetic neuropathy score (MDNS) and Nerve conduction study (NCS) were assessed. Results: CPT scores in the DPN group were consistently higher than that in the Non-DPN group on both upper and lower extremities ($P<0.05$). Significantly positive correlation was observed between CPT and individual NCS parameters as well as MDNS score ($P<0.001$), with CPT score showing a high correlation with sural velocity ($r = 0.71$, $P<0.001$). The area under the ROC curve (AUC) of CPT on left lower extremity was 0.930, higher than that of MDNS (0.914); CPT value on left lower extremity showed higher specificity (90%) than the MDNS (80.2%) scales. ROC represented the two clinical scales that showed the best specificities in identifying neuropathy: CPT and MDNS. Conclusions: PainVision™, a non-invasive and quick test, could be used as an objective screening method for DPN in busy diabetic clinics, ensuring adherence to the current unfulfilled recommendations of annual assessments for all diabetic patients.

Keywords: Diabetic peripheral neuropathy, PainVision™, current perception threshold, nerve conduction velocity

Introduction

Diabetes mellitus (DM) is a worldwide epidemic; 246 million adults had diabetes mellitus in 2008, a number expected to reach 380 million in 2025 [1]. Consistently, type 2 diabetes mellitus (T2DM) rate is increasing, and likely attributable to rapid economic development, improved living standards, aging population, obesity, and lack of exercise [2]. Diabetic peripheral neuropathy (DPN) is the most common long-term complication of T2DM and affects approximately half of the patients over the course of disease; it is also known as symmetrical and length-dependent sensorimotor polyneuropathy [3]. It is well recognized that DPN has major impacts on quality of life, morbidity, and mortality, with considerable health care costs [4, 5]. Owing to diabetic patients sustaining extensive nerve damage and peripheral nerve dysfunction without any overt symptoms in the early disease stage, DPN has become a serious global health problem. In clinical practice, neuropathy assessment is based on questionnaires, clinical evaluation, and electro-diagnostic tests [6]; these methods are primarily aimed at screening for DPN risk, and tend to diagnose the disease when it is well established. Moreover, these clinical tests rely on the subject's cognitive function and are not objective. Late diagnosis hampers the focus on early and intensified diabetes control, as well as the prevention of neuropathy-related sequelae [7]. In addition, DPN diagnosis is not always reproducible, even when performed by experts [8].

An early manifestation of distal small and large fiber neuropathy may be involved in DPN [9]; nerve fiber damage causes many symptoms, including numbness, tingling, and burning sensation in the legs and hands. Ultimately, muscle weakness, loss of reflexes, and foot deformities

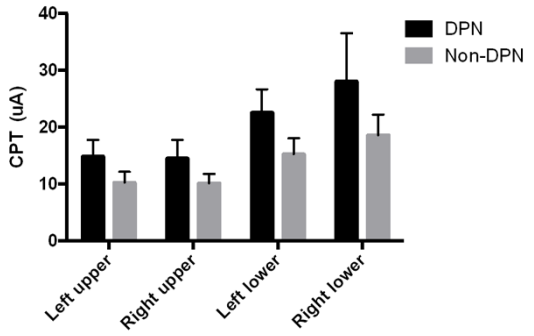

Figure 1. Distribution of CPT scores in each group. CPT: current perception threshold; DPN: diabetic polyneuropathy; Non-DPN: non-neuropathic diabetes mellitus.

can result, leading to end clinical sequelae of ulcers, potential infection, erectile dysfunction, autonomic dysfunction, and amputation for some patients with poorly controlled disease. Nerve conduction study (NCS) is considered the reference standard in diagnosing DPN, because of the advantages of objectivity, sensitivity and reliability [10]. It consists of both nerve conduction velocity (NCV) and needle electromyogram (EMG). The EMG test can detect the neuropathy, excited muscle, and conduction function. However, this test is often associated with time consumption, high cost, the need for professional operators, and usually an aggressive feeling, which limit its use in perioperative patients. This highlights the urgent need for an objective, quantitative screening test for DPN in clinical practice that overcomes the limitations of current methods.

A newly developed device, PainVision™ PS-2100 (Nipro, Osaka, Japan), has been used to provide a quick, non-invasive, reproducible, and quantitative assessment of peripheral nerve function [11, 12]. Current perception threshold (CPT) is the minimum electrical stimulation felt by patients. CPT measurement is based on an electrical stimulus attached to the medial forearm (**Figure 1**) with the application of an electrode gel. The subjects themselves compared the degree of sensation after electrical stimulation. The electrical current intensity is recorded as the CPT, with three measurements carried out within a 5-minute interval and averaged. To our knowledge, no previous report on PainVision™ use for DPN assessment has been published. Hence, the aim of this study performed in subjects with T2DM was to evaluate whether PainVision™ can reliably screen for DPN carefully characterized by nerve conduction assays according to American Academy of Neurology guidelines.

Materials and methods

Ethics statement

This prospective randomized study was conducted from July to November 2013 in patients at the Endocrinology Department of East Hospital Affiliated to Tongji University (Shanghai). It was approved by the Regional Ethics Committee, and informed consent was obtained from all patients before enrolment. This study was registered at the Health Bureau of Shanghai Pudong.

Study design

The American diabetes association (ADA) type 2 diabetes diagnostic criteria [13] were used for T2DM diagnosis. A total of 49 T2DM subjects (24 males and 25 females; mean age of 61.96±9.269 years; disease course of 5-30 years) with peripheral neuropathy were enrolled as the DPN group. Inclusion criteria for DPN patients were [14]: clinical manifestation with acroparesthesia or motor nerve involvement; reduced degree of deep and superficial sensation; reduced sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MCV) in electromyography (EMG). In addition, 43 non-diabetic subjects (Fasting plasma glucose <7.0 mmol/L; postprandial blood glucose <11.1 mmol/L) without organic disease of the nervous system, and specifically matched by gender, age, and body mass index (BMI) were assigned to the Non-DPN group. Subjects were excluded with mental disorder or instability problems that made it impossible to understand the concepts of CPT and MDNS, any trauma, lumbocrural pain, nerve muscle joint or muscle disease, and/or peripheral neuropathy caused by any other condition.

Outcome

Baseline characteristics of the study subjects were recorded, including gender, age, body mass index (BMI), Waist-to-Hip Ratio, and diabetes duration. Laboratory testing included Fasting blood glucose (FBG) and Glycosylated hemoglobin a1c (HbA1c) assay, performed on a

CXII Beckman automatic analyzer. In addition, all subjects were evaluated by the MDNS system; CPT was measured by using the PainVision™ system, while NCV was assessed by Electromyography.

Michigan diabetic neuropathy score (MDNS)

Neurological examination was performed according to the structured, validated Michigan diabetic neuropathy score (MDNS) questionnaire [15]. The scales were administered, using a standardized protocol, at the same time in each subject to allow for between scale comparisons: (1) sensory loss (10 gram Semmes Weinstein type monofilament testing on the hallux [The monofilament tip was gently applied to the skin, bent slowly to approximately 3/4 of its extended length, and slowly released. The application occurs within approximately 2 seconds], vibration testing using a Rydel-Seiffer tuning fork on the hallux interphalangeal joint, pin perception on the hallux using a nickel-plated steel (size #2 safety pins), cold perception using metal thermal disks on the foot dorsum; (2) ankle reflexes were graded as reduced if they can only be obtained with reinforcement, and absent if they cannot be obtained with reinforcement. Evaluation of each parameter was carried out at both sides, with 0, 1, and 2 given for normal, reduced, and absent results, respectively. Descriptors were rated on an intensity scale (0-6, none; 7-12, mild; 13-29, moderate; 30-48, severe); higher numbers indicate more severe neuropathy.

Painvision™ Principle of CPT determination

PainVision™ (PV, PS-2100; Nipro Co., Osaka, Japan) is a medical tool used for the quantitative analysis of pain perception and sensation; it has recently been introduced in the field of pain clinics and anesthesiology [11, 16-18]. The PainVision™ system consists of four devices: (1) the main PainVision™ system unit, (2) a personal computer connected to the PainVision™ system, (3) sensors with a hand switch, and (4) a specialized disposable EL-BAND. The specific protocol for using the system is as follows: First, the EL-BAND that transmits the electrical current is attached to the left medial forearm (**Figure 1**) with the application of an electrode gel (contact resistance of about 10 kΩ). The medial forearm was selected for the EL-BAND attachment site because of its thin skin, flat surface, low distribution of sweat glands and hair follicles, and the resulting high sensitivity of electrical stimulation and good electrical conductance. The electrical stimulus is amplified sequentially from low intensity current (50 Hz, 0-150 μA RMS, pulse width 0.3 ms). The subjects themselves compared the sensation degree of the electrical stimulus. Each subject was instructed to press the button on the hand switch with any subtle sensation perceived at the EL-BAND attachment site. The current perception threshold (CPT), defined as the minimum electrical stimulation sensed by the subject, was measured three times within a 5-minute interval, and averaged values were obtained. In this method, heterogeneous perceptions and senses are aroused by electrical stimulation, and were evaluated quantitatively for perception threshold as felt by a subject. However, both medial forearm sides and the front of the ankle in lower extremities were selected as EL-BAND attachment sites.

Nerve conduction study (NCS)

Nerve conduction studies were performed in this study as the gold standard for DPN diagnosis. The electrodiagnostic assessment was carried out on a two-channel EMG device (Medelec Oxford, UK). All patients underwent sensory and motor NCS of the sural sensory nerve and peroneal nerve in left lower extremities, according to the American Association of Electrodiagnostic Medicine guideline [19], to explore large nerve fiber function. In this study, only left side extremities were assessed in order to reduce invasive damage to patients. Detection indexes included nerve distal latency, amplitude and velocity. Electrophysiological tests were performed in a warm room with the subject maintaining a temperature above 31°C. The protocol included: (1) Sensory NCS of sural nerve action potential and conduction velocities; and (2) Motor NCS of common peroneal nerve compound muscle action potential, conduction velocity and distal latency. Based on NCS and EMG findings compared with the normal values in our department, DPN was confirmed or excluded in each patient.

Statistical analyses

All statistical analyses were performed using the SPSS program version 22.0 (SPSS Inc., Chicago, IL). Continuous variables with normal distribution were expressed as mean ± stan-

Table 1. Participant characteristics

Anthropometric parameters	DPN (n = 49)	Non-DPN (n = 43)
Gender (M/F)	24/25	18/25
Age (years)	61.96±9.269	61.42±10.509
BMI (kg/cm^2)	26.44±3.93*	23.56±3.27
Waist-to-Hip Ratio	0.95±0.08*	0.91±0.06
Diabetic characteristics	Range or limit of normal	
Duration of DM (years)	11.04±7.12	---
Duration of DPN (years)	7.6±6.1	---
FPG (mmol/L)	12.97±5.49	<11.1
HbA1c (%)	9.23±2.1	<6.0
CPT Upper extremities		
The left	14.89±2.85*	10.27±1.89
The right	14.52±3.23*	10.16±1.63
CPT Lower extremities		
The left	22.55±4.10*	15.26±2.79
The right	28.06±8.45$^\Delta$	18.62±3.60
MDNS Score	10.71±6.13$^\Delta$	2.63±1.54
Nerve conduction studies		
Sural Velocity (m/v)	44.88±3.40$^\Delta$	51.46±3.50
Sural Amplitude (mv)	9.10±3.96$^\Delta$	25.37±6.64
Peroneal Velocity (m/s)	40.82±4.98$^\Delta$	48.09±3.56
Peroneal Amplitude (mv)	3.96±1.53$^\Delta$	10.41±2.47
Peroneal Distal Latency (ms)	4.08±0.92	4.13±0.81

DPN: diabetic peripheral neuropathy; Non-DPN: non-diabetic peripheral neuropathy; BMI: body mass index; CPT: the current perception threshold; MDNS: Michigan diabetic neuropathy score. *Denotes significant difference between groups (P<0.05). $^\Delta$Denotes significant difference between groups (P<0.01).

Table 2. Correlation of PainVision measures with CPT, NCS and MDNS score

	r	*P* value
Sural Velocity (m/v)	0.46	<0.001
Sural Amplitude (mv)	0.71	<0.001
Peroneal Velocity (m/s)	0.62	<0.001
Peroneal Amplitude (mv)	0.57	<0.001
Peroneal Distal Latency (ms)	0.23	0.116
MDNS Score	0.54	<0.001

CPT: the current perception threshold; MDNS: Michigan diabetic neuropathy score; NCS: Nerve conduction studies.

dard deviation (SD). Student's t-test was used to assess differences between two groups of continuous variables. The associations of CPT with NCV and MDNS scores were assessed by Spearman's rank correlation analysis. Receiver operating characteristic (ROC) curves were generated and compared as previously described (DeLong, DeLong, & Clarke-Pearson, 1988). P< 0.05 was considered statistically significant.

Results

General clinical features of the subjects

A total of 92 subjects, 49 DPN patients and 43 non-DPN patients, were included in this study. **Table 1** summarizes their demographic and diabetic characteristics, as well as CPT and MDNS examined neuropathy scales and nerve conduction studies. No significant differences were observed in gender (P>0.05) and age (P>0.05) between groups. The DPN group had significantly higher BMI (P<0.05) and Waist-to-Hip Ratio (P<0.05) compared with the Non-DPN group. DPN group patients had consistently significantly greater CPT scores (P<0.05) compared with the Non-DPN group on both upper and lower extremities, as shown in **Figure 1**.

Correlations between CPT, MDSN score and Nerve conduction studies

Owing to the NCS test performed on left extremities, CPT score on left lower extremities was selected for correlation analyses. Based on Spearman's rank correlation analysis, significantly positive correlations were observed between CPT and individual NCS test and MDNS parameters. As shown in **Table 2**, CPT scores showed high correlations with sural velocity (r = 0.46, P<0.001), sural amplitude (r = 0.71, P<0.001), peroneal velocity (r = 0.62, P<0.001), peroneal amplitude (r = 0.71, P< 0.001) and MDNS scores (r = 0.54, P<0.001). However, no correlation was obtained between CPT and peroneal distal latency (r = 0.23, P = 0.116).

ROC for clinical neuropathy scales

Table 3 shows ROC curve data and scores in two clinical neuropathy scales for subjects with T2DM associated DPN and normal controls. Cutoff, sensitivity, specificity, area under the

Table 3. Comparison between ROC for different types of neuropathy

Measurement Scale	Cutoff (μA)	Sensitivity (%)	Specificity (%)	Area (95% CI)
Left upper	12.2	0.834	0.875	0.917 (0.864~0.971)
Right uppe	13.1	0.673	0.975	0.910 (0.852~0.967)
Left lower	18.8	0.838	0.900	0.930 (0.882~0.978)
Right lower	21.2	0.827	0.825	0.902 (0.841~0.963)
MDNS Score	---	0.865	0.802	0.914 (0.859~0.969)

ROC: Receiver operating characteristic; MDNS: Michigan diabetic neuropathy score; NCS: Nerve conduction studies.

curve (AUC), and 95% CI were recorded. The bigger the area under a curve, the higher the corresponding diagnostic accuracy, which indicated the CPT test had the highest DPN diagnositic value. As shown in **Table 3** and **Figure 2**, the AUC of CPT on left lower extremities was greater (0.930) with a higher specificity (90%), compared with that of MDNS (0.914), with a specificity of 80.2%. The CPT score on right upper extremities had the best specificity (97.5%) but lowest sensitivity (67.3%). The MDNS score had the best sensitivity (86.5%). In addition, the CPT of right lower extremities had the smallest AUC (0.902), with sensitivity and specificity of 0.827% and 0.825%, respectively. The CPT of left upper extremities had an AUC of 0.917, with sensitivity and specificity of 0.834% and 0.875%, respectively. Cutoff points could be used to detect subjects with neuropathy from control subjects. ROC cutoff points analysis indicated that CPT scores on lower extremities were consistently higher than those obtained for upper extremities, among which the cutoff points on right lower extremities were the biggest (21.2 μA). All scales showed an excellent accuracy in discriminating between subjects with neuropathy and the Non-DPN group.

Discussion

Diabetic peripheral neuropathy (DPN) is a frequent complication in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) patients, affecting approximately 54% individuals with diabetes [20]. In addition, neuropathy is often detected when very well established and consequently impossible to reverse; it is indeed very challenging to halt the inexorable neuropathic process. Many DPN patients end up in a foot clinic and have a very poor outcome, with 5-year mortality close to 50% [21]. Hence, screening and early diagnosis of DPN would provide a crucial opportunity for these patients with DM to judge disease progression. So far, no efficient quantitative early marker of DPN is available in our busy diabetic clinic. We routinely use measures such as clinical questionnaires or peripheral neurological examination using other bedside instruments are an important component in evaluating patients with suspected peripheral nerve disorders. However, these methods are crude, invasive, time-consuming, or detect the disease at a very late stage. Clearly, the development of non-invasive, quick and sensitive measures of neuropathy is urgently needed.

In this study, we demonstrated that PainVision is a reliable device for detecting DPN by comparing the diagnostic capabilities of CPT, NCS test and MDNS in patients with T2DM, according to American Academy of Neurology recommendations [14] as reference standard. As shown above, the CPT of left upper extremities was 14.89±2.85 μA in the DPN group, larger compared with that of the Non-DPN group (10.27±1.89 μA), corroborating a study by Japanese researchers. Sado *et al.* [22] assessed a total of 747 subjects, including DPN and normal controls, and found CPT of 12.3±5.4 μA in the DPN group, lager than that of the Non-DPN group (9.5±3.7 μA). In addition, we measured the CPT scoring on the right medial forearm, and the front of the ankle in both lower extremities. There was consistently significant differences compared with the control group ($P<0.01$); the CPT score in the DPN group was higher than that of the Non-DPN group. In addition, subjects with DPN had higher waist-to-hip values compared with those without DPN. Similarly, Wagner *et al*. [23] suggested higher waist-to-hip is a potential independent risk factor for DPN, and associated with lower heart rate variability (HRV). Out finding indicated a strong correlation between the CPT on left lower extremities and individual parameters of NCS test (sural velocity, sural amplitude, peroneal velocity and peroneal amplitude) and MDNS score ($P<0.001$), but no association with peroneal distal latency score. These results indicate a close association between severity

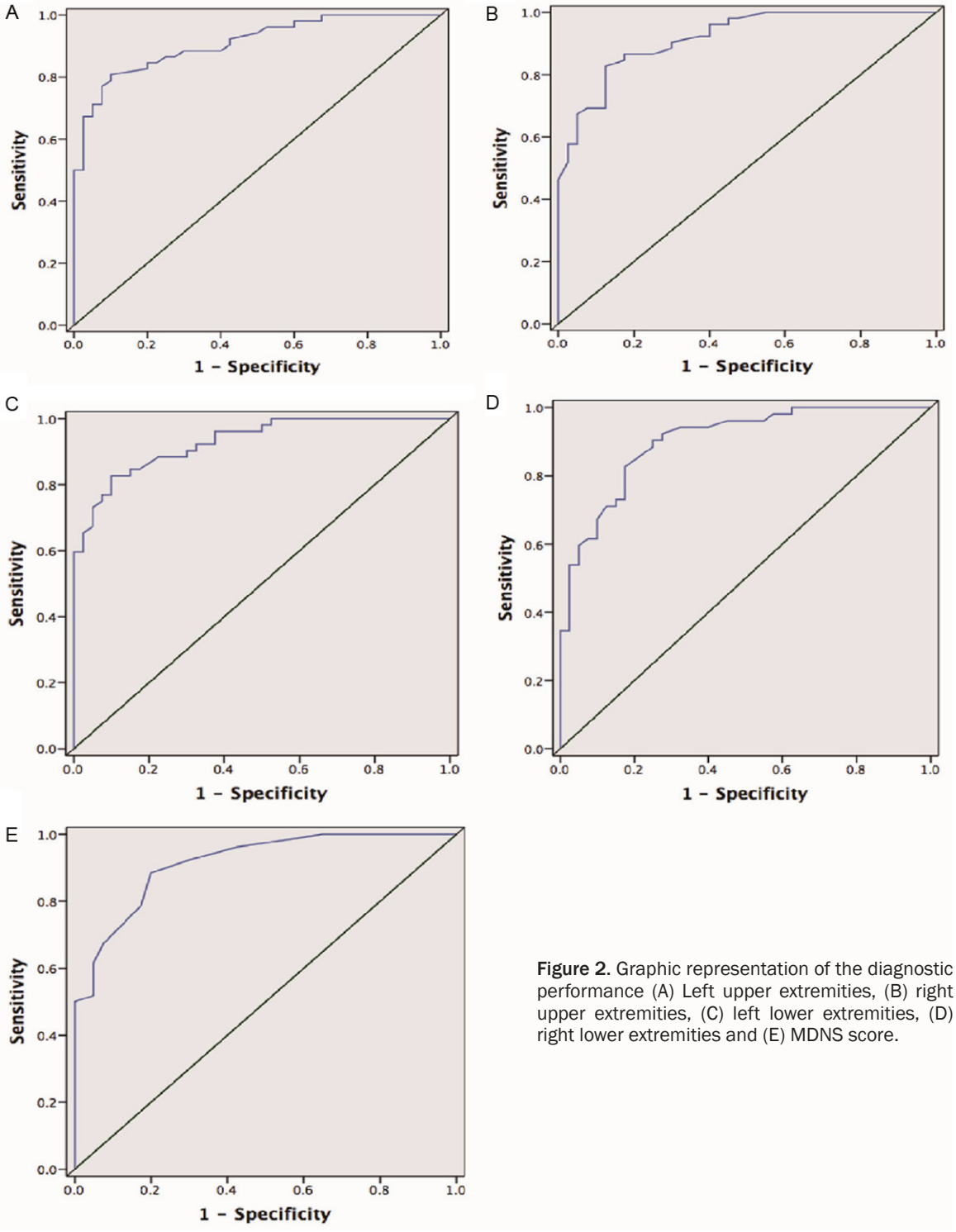

Figure 2. Graphic representation of the diagnostic performance (A) Left upper extremities, (B) right upper extremities, (C) left lower extremities, (D) right lower extremities and (E) MDNS score.

of PainVision™ measures and neuropathy severity parameters. The area under the ROC curve showed a significant result for the CPT (0.93) on left lower extremities with a sensitivity of 83.8% and specificity of 90%, better than that obtained for the AUC of MDNS (0.914) and CPT scores on the other extremities. The ROC cutoff points of CPT scores on lower extremities were consistently higher than upper extremity counterparts, which may be associated with different skin sensitivity; indeed, sensitivity of lower extremity skin is significantly worse than

that of upper extremities. Therefore, the CPT score is more effective for early diagnosis of neuropathy than the MDNS test, apart from convenience and repetitive diagnosis of the PainVision™ device.

A number of recent studies have assessed the potential utility of PainVision™ as a system for quantitating perception and pain, and this tool has recently been used in pain clinics [16, 18, 24]. A study of recently diagnosed type 2 diabetic patients found that early nerve damage in diabetic patients was characterized by involvement of both small and large fibers [9]. PainVision™ gives patients an alternative painless sensory stimulation, mainly by stimulating sensory nerve fibers Aβ and Aδ, measuring the intensity of the stimulation. This device has been used in studies on persistent chronic pain, such as herpes zoster-associated pain [18], and procedural pain, such as wound dressing removal [24] In these studies, reproducibility and validity of PainVision™ were confirmed. To our knowledge, no previous report is available assessing neuropathy of DPN using such electrical stimulation, or nerve conduction. Thus, our findings corroborate other recent studies. Even though the number of patients included in this study was small, all underwent careful characterization for peripheral neuropathy using Gold standard AAN criteria [14].

Currently, a number of validated methods have been assessed for diagnosis and screening of DPN [25-27]. However, none is suitable for use in busy diabetic clinics due to requirement of very specialized equipment, complicated patient preparation, highly trained technicians for test performance, and time consumption [28]. The potential use of PainVision™ appears to address all these shortcomings, as it is completely non-invasive, can be performed in less than 5 minutes, and specialist training is not necessary. PainVision™ provides a ready objective and quantitative measure of DPN, which is particularly appealing, allowing the assessment of disease progression.

In conclusion, this study suggests that PainVision™ is completely convenient, with no special position requirements, and no adverse events or discomfort during and after measurement. Peripheral neuropathy function can be evaluated using the CPT test of PainVision™, which is a reliable, objective and quantitative method, and may be included as a screening tool for DPN.

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Disclosure of conflict of interest

None.

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