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EDITORIAL

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1. Introduction

Diabetic polyneuropathy (DPN) is the most common chronic complication of diabetes mellitus (DM) [1], affecting approximately 20% of community patients [2], whereas it is increasingly appreciated that it is also present in a substantial percentage of patients with prediabetes [3]. It is predictably associated with significant comorbidities including lower leg amputation, depression, and cardiovascular disease [2]. However, despite a majority of diagnostic tools [1], underdiagnosis of DPN remains a serious concern, especially in the primary care setting [4]. Consequently, interest has focused on development of new modalities including a number of bedside tests [5], as well as more sophisticated methods, such as skin biopsy and corneal confocal microscopy [6].

Among these new diagnostic methods, NC-stat ®/DPNCheck™, a novel point-of-care, portable, noninvasive device for automated nerve conduction study (NCS), manufactured by NeuroMetrix Inc. (Waltham, MA) is very promising [7]. This apparatus is fully integrated, in contrast to an earlier alternate version (NC-stat® by the same manufacturer), which included a remote on-call information system that received, interpreted, and then transmitted to physician's office patient NCS data [7,8]. The new device is designated to report two conduction parameters, namely sural nerve conduction velocity (SNCV) (latency to the initial positive peak) measured in meters per second (m/s), and sural nerve amplitude potential (SNAP) (baseline to initial negative peak) measured in microvolts (µV) [7].

2. Testing protocol

The novel NC-stat®/DPNCheck™ device consists of a single handheld unit which is placed on the lateral aspect of the patient's lower leg such that the two stimulation (stainless steel) probes contact the leg just posterior to the lateral malleolous whereas the disposable biosensor, which records the sural response, is at a fixed distance of 9.22 cm proximal to the stimulating probes at the opposite end of the device, contacting the patient's lower calf [7]. More specifically, the largest probe is placed halfway between Achilles tendon and the lateral malleolus over the anatomical position of the sural nerve (anterior to the Achilles tendon and posterior to the lateral malleolus). As a result, the biosensor is found in the lower calf in line with Achilles tendon. Before test initiation, test area should be scrubbed and conductive gel should be applied to each probe.

Just below the stimulating probes, an infrared thermometer is responsible for detection of ankle temperature. Thereby, automatic correction for skin temperature is achieved, compensating for SNCV with a linear temperature compensation factor of 1 m/s per °C (with a reference temperature of 28°C) and preventing beginning of tests when ankle temperatures are below 23°C (in this case the test will stop with °C displayed on the screen) [7]. Compensation is not applied on SNAP due to the more restricted effect of temperature on this parameter [7]. On the opposite of the probes and biosensor, a display screen and a single button is found. Once the button is pressed, test is initiated and orthodromical nerve stimulation (between 4 and 16 times within 10–20 s) occurs [7]. SNAP is measured peak to peak and SNCV is measured to the onset of the initial negative deflection [9]. Results below 1.5 µV are automatically adjusted to zero by the device [7].

Importantly, the biosensor covers a wide area to allow automated search of the clearest measurement signal. Mean duration of procedure is generally 15–30 s for each lower extremity. More importantly, the test can be performed by nonexpertise personnel after only 30–60 min training [7]. However, correct device setting and patient positioning that is steady and allows firm pressure of the biosensor and the probes alongside with adequate skin preparation and sufficient gel in probes is crucial [9]. It is undoubtedly true for NC-stat®/DPNCheck™ that, like any other medical device, the ultimate value reflects the degree of 'careful' attention required.

Accordingly, it is of particular significance to underline that visual review of the sural response waveform and verification of its parameters in real time is also available to the physician before acceptance of a recordable response [10]. This information (which requires a degree of special training) is of particular importance for most electrophysiologists familiar with the use and interpretation of such measurements (especially for reproducible surface sural response recordings of 2–4 µV that require experience and attention to such technical details) and

represents a major improvement on existing handheld devices.

3. The first NC-stat® device

Konq et al. [8] applied the first NC-stat® device to the median, ulnar, peroneal, and tibial nerves of healthy volunteers without neuropathic symptoms. Reproducibility (tested on the median and ulnar sensory nerves) compared favorably with traditional electromyography laboratories [8]. However, it should be underlined that the sensory nerves (median and ulnar) evaluated in this study have robust amplitudes, typically much higher than the sural nerve amplitude [11], whereas only the results of correlational analyses involving a small number of subjects were included, with the average day-to-day amplitude change tabulated for these nerves, not the individual values [8]. Thus, verification of reproducibility of the individual values is needed from larger studies evaluating application of the device on the sural nerve of DM patients.

In patients with type 1 and type 2 DM, this original device again resulted in reasonable agreement with conventional NCS parameters (the reference standard) performed by electromyography technicians, and it could accurately identify DPN in both type 1 and type 2 DM patients [12,13]. Spearman coefficients for correlation between the SNAP of the point-of-care and conventional NCS was high: 0.95 (with p < 0.001) [12]. However, Bland and Altman statistical method showed a slight underestimation of SNAP by an average of 1.2 ± 3.4 µV with the point-of-care device in comparison with the reference method [12]. In spite of this systematic bias (which is reported as clinically unimportant by the authors), quantitative agreement as demonstrated by the Bland and Altman method was strong [12]. Specifically, this novel device resulted in sufficient sensitivity and specificity of 88% and 82%, respectively [13].

A cross-sectional study of 195 patients with long-standing type 1 DM provided the opportunity to examine the sensitivity, specificity, Youden's Index, positive (PPV) and negative predictive value (NPV) of the early NC-stat device, as well as of other assessment modalities, namely Vibratron II Device, Michigan Neuropathy Screening Index (MNSI), and monofilament, for detection of an abnormal NC-stat outcome [14]. NC-stat® (and specifically SNAP) detected clinically diagnosed DPN with 79% sensitivity, 48% specificity, 54% PPV, 74% NPV, and 0.27 Youden's J Index. Furthermore, all patients with an abnormal monofilament test also exhibited abnormal sural nerve conduction (PPV 100%), whereas 60% of patients with a negative monofilament test had neuropathy as defined by abnormal sural nerve conduction (NPV 40%) [14]. The corresponding PPV for Vibratron II and MNSI was 69% and 77%, respectively. NPV was 58% and 61%, respectively [14].

4. The novel NC-stat®/DPNCheck™ device

The novel NC-stat®/DPNCheck™ device was assessed in a cohort of 16 type 1 and 28 type 2 DM patients with mean age 56 ± 18 years and mean DM duration 18 ± 14 years [7]. Subjects received standard NCS measurements on the left lower limb using the Sierra Wave instrument (Cadwell Laboratories, Kennewick, WA, USA) and bilateral examination on the lower limbs by two raters with NC-stat®/DPNCheck™. Intra- and interobserver reliability was assessed using intra-class correlation coefficients (correlation coefficients >0.75 were considered to have excellent reliability). NC-stat®/DPNCheck™ exhibited excellent intra-observer (correlation coefficients: 0.97 and 0.94 for SNAP and SNCV, respectively) and interobserver reproducibility (correlation coefficients: 0.83 and 0.79 for SNAP and SNCV, respectively), quite comparable with standard NCS [7]. In comparison with standard NCS, quantitative accuracy with the novel device was excellent for SNAP (mean bias: −0.1 ± 3.6 µV), but substantially impaired for SNCV (+8.4 ± 6.4 m/s) [7]. Nonetheless, this did not interfere with the ability to identify DPN with high sensitivity (95%) and acceptable specificity (71%) [7].

We have also provided evidence of the diagnostic accuracy of NC-stat®/DPNCheck™, especially in exclusion of DPN [15]. We compared the NC-stat®/DPNCheck™ device with the standardized clinical examination score Neuropathy Disability Score (NDS), in 114 type 2 DM patients and 46 age- and sex-matched controls. DPN was defined as NDS ≥3 [15]. NC-stat®/DPNCheck™ yielded excellent sensitivity (90.48%) and NPV (93.94%) along with high specificity (86.11%) and PPV (79.17%), Youden's J being as high as 0.77 [15]. A very good negative likelihood ratio of 0.11 was also demonstrated [15].

Another study investigated the utility of NC-stat®/DPNCheck™ NC in staging DPN, in comparison with the clinical NDS [16]. Additionally, NC-stat®/DPNCheck™ was compared with the laser Doppler (LDI) $_{FLARE}$ technique, an established method for early evaluation of small nerve fiber dysfunction [16]. In this study, 80 healthy controls with mean age 39.67 ± 15.17 years and 162 DM patients (80 type 1 and 82 type 2 DM patients) with mean age 47.96 ± 13.98 years and mean diabetes duration 11.4 ± 9.4 years were included. Subjects were categorized into those with none (NDS 0–2), mild (NDS 3–5), moderate (NDS 6, 7), and severe DPN (NDS 8–10) [16]. In all DPN stages, SNAP and SNCV as measured with NC-stat®/DPNCheck™ correlated significantly with LDI$_{FLARE}$ (r < 0.90 and r = 0.78 for SNCV in healthy controls and DM patients, respectively; r = 0.88 and r = 0.73, for SNAP in healthy controls and DM patients, respectively) [16]. It is particularly of interest that good correlation between the two parameters measured with NC-stat®/DPNCheck™ and the LDI$_{FLARE}$ was also seen in subjects without clinical neuropathy (NCS 0–2), thereby suggesting that the device might be helpful in assessing progression in individuals even at the early stages of neuropathy. However, it should be underlined that the NC-stat®/DPNCheck™ device measures only large fiber neural function and the sural response measurements do not reflect small nerve fiber integrity. This study actually provided evidence of significant linear relationships between NC-stat®/DPNCheck™ (with both comparators), the LDI$_{FLARE}$ technique, and clinical neuropathy scores [16]. Thus, the clinical implication is that the novel NC-stat/DPNCheck™ device could serve as adjunctive diagnostic tool for diagnosing DPN in the clinical setting.

Clearly, the NC-stat®/DPNCheck™ is very promising. However, some limitations must be borne in mind. The first is variation of SNAP and SNCV from test to test [8]. This might

derive from differences in device placement or nearby electrical interference, but in general, acceptable limit by NeuroMetrix Inc. is considered a variation of less than 5% for SNCV and less than 25% for SNAP [17]. The clinical implication of this is that a borderline result should be repeated. Second, a small systematic bias for SNAP [12] or SNCV measurement has been reported [7]. A third limitation relates to a number of reasons, such as anatomical variations of sural nerve, severe edema, excessive adipose tissue, poor skin preparation and device misplacement, which might produce non-recordable measurements (SNAP less than 1.5 μV). Thus, in case of a 'zero' result, differentiation between severe DPN and nonclinical causes (especially anatomical variance of the sural nerve) is not always easy, and so, if electrophysiological confirmation is required, patients with signs or symptoms suggestive of DPN should be referred to established NCS and/or expert clinical examination [16].

Furthermore, temperature slightly affects SNCV (SNCV is reduced by nearly 2 m/sec per °C temperature fall) [18] and SNAP (albeit in a favorable direction, with cooler temperatures producing larger amplitudes) [9], which may be solved by mathematical SNCV compensation for temperatures below 30°C [9]. In addition, we are looking forward to longitudinal and cost-effectiveness studies along with future works comparing with conventional and gold standard tests as well as the ability of the device to monitor progression of neuropathy and therapeutic response, because such works will be able to prove the safety and efficacy of this technology.

Additionally, results of NC-stat®/DPNCheck™, like any other instrument that provides descriptive measures of a parameter that relates to a certain condition, provide descriptive measures of the sural nerve action potential [7], and it is only in the proper setting that an abnormal sural response may electrodiagnostically confirm an underlying sensory polyneuropathy, which, in turn, could be due to diabetes.

To date, the most common tools that are implicated in DPN diagnosis are the 128 Hz vibration tuning fork and the 10-gm Semmes-Weinstein monofilament which however detect only advanced, large fiber neuropathy [14,16]. Furthermore, national institute for clinical excellence (NICE) recommendations for lower limb neuropathy of T2DM patients in the primary care setting implicate the two aforementioned tools alongside with palpation of foot pulses and inspection for foot deformity and of footwear, whereas there is currently no standardized test in the primary care setting to test for early stages of peripheral neuropathy [19]. Additionally, clinical examination relies importantly on patient feedback [7], whereas application of the gold standard NCS is limited by restricted availability and device complexity [14,15].

Hence, NC-stat®/DPNCheck™ harbors very useful characteristics: (1) it exhibits high reproducibility [7]; (2) its results in confirming vs. excluding DPN correlate well with conventional NCS [7, 12, 13] and clinical NDS [15]; (3) it additionally detects DPN in up to 60% of patients with a negative monofilament test [14]; (4) its application is not restricted by physician's subjective interpretation or by inadequate patient cooperation [15]; (5) it can be easily performed by nontechnical personnel after very brief training [7,20]. Nonetheless, impaired sural nerve function is not always by definition attributable to DM,

and other causes of sensory polyneuropathy may have to be excluded, as, indeed, with any other diagnostic tool of DPN.

In conclusion, the NC-stat®/DPNCheck™ device provides important improvements, such as the ability to visually inspect the sural response waveform [10], which are undoubtedly of service for any experienced electrophysiologist, both in screening and in follow-up of DPN. However, it is the authors' recommendation that NC-stat®/DPNCheck™ could play an important role, especially in the primary care setting, as a screening tool for DPN although clearly, more clinical experience is highly welcome.

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Declaration of interest

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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