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Validation of cooling detection threshold as a marker of sensorimotor polyneuropathy in type 2 diabetes

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ABSTRACT

Aim: We aimed to validate the performance cooling detection thresholds (CDT) to detect diabetic sensorimotor polyneuropathy (DSP) in type 2 diabetes.
Methods: Two hundred and twenty participants with type 2 diabetes underwent clinical and electrophysiological examinations including 3 small fiber function tests: CDT, heart rate variability (HRV) and LDI_{FLARE}. Clinical DSP was defined by consensus criteria whereas preclinical DSP was defined by presence of at least one electrophysiological abnormality. Area under the curve (AUC) and optimal thresholds were determined by receiver operating characteristic curves.
Results: Participants were aged 63 ± 11 years with mean HbA1c of 7.5 ± 1.6%. The 139 (63%) clinical DSP cases had mean CDT values of 18.3 ± 8.9 °C; the 52 (24%) preclinical DSP cases had 25.3 ± 3.5 °C; and the 29 (13%) controls had 27.1 ± 3.8 °C; (p-value < 0.02 for all comparisons). For identification of clinical DSP cases, AUC_{CDT} was 0.79 which exceeded AUC_{HRV} (0.60, p = <0.0001) and $AUC_{LDI\ FLARE}$ (0.69, p = 0.0003), optimal threshold <22.8 °C (64% sensitivity, 83% specificity). Preclinical DSP AUC_{CDT} was 0.80, also exceeding the other 2 measures (p < 0.02 for both comparisons), optimal threshold ≤27.5 °C (83% sensitivity, 72% specificity).
Conclusions: CDT had good diagnostic performance for identification of both clinical and preclinical neuropathy in type 2 diabetes. Its use as a non-invasive screening tool should be considered for research and clinical practice.

1. Introduction

Diabetic sensorimotor polyneuropathy (DSP) is a chronic, symmetrical, length-dependent neuropathy that likely represents the most common complication of diabetes (Tesfaye et al., 2010). With an annual incidence of 2% in diabetes patients (The Diabetes Control and Complications Trial Research Group, 1993), it accounts for significant morbidity, mainly associated with foot ulceration and limb loss (Driver, Fabbi, Lavery, & Gibbons, 2010), and is responsible for a striking 50–75% of non-traumatic amputations (Most & Sinnock, 1983; Pecoraro, Reiber, & Burgess, 1990). It therefore represents a huge economic burden, with annual health costs estimated at $10.9 billion in the US (Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003). Disease modifying drugs are yet to be developed (Duby, Campbell, Setter, White, & Rasmussen, 2004), and the main treatment modality remains the achievement of target glycemic control - an intervention likely best accomplished early on in the disease process when it is most amenable to treatment.

Current methods to screen for DSP include assessment of vibration sensation (using, for example, the 128 Hz tuning fork) and tactile sensation (using, for example, the 10 g Semmes-Weinstein monofilament); however, these physical examination tests are limited by intrinsic factors such as insufficient reproducibility (Dyck et al., 2010; Perkins, Olaleye, Zinman, & Bril, 2001). Another limitation of these tools is that they primarily detect large fiber dysfunction and since the prevailing hypothesis is that DSP is known to affect small fibers of the Aδ and C type - which carry pain and thermal sensation - before large fibers (Divisova et al., 2012; Jimenez-Cohl, Grekin, Leyton, Vargas, & Villaseca, 2012), screening tools that quantitatively detect dysfunction in smaller nerve fibers have become a focus for diagnosing early DSP. The gold standard measure for this is intra-epidermal nerve fiber density via skin punch biopsy (Devigili et al., 2008; Lauria et al., 2010), but its use is limited by its invasive nature. Corneal confocal microscopy represents a non-invasive alternative that is under active research, but evaluation of training expertise and cost are currently in progress (Ahmed et al., 2012; Quattrini et al., 2007; Tavakoli et al., 2010).

Conflicts of interest: B.A.P. has received speaker honoraria from Medtronic Inc., Johnson and Johnson, Roche, GlaxoSmithKline Canada, Novo Nordisk and Sanofi; has received research grant support from Medtronic and Boehringer Ingelheim; and serves as a consultant for Neurometrix. All other authors report no potential conflicts of interest.

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Functional assessment using sensory measures of thermal thresholds is a non-invasive way to quantitatively and selectively measure small fiber damage. This includes measurement of cooling detection threshold (CDT), which evaluates the perception of cold stimulus. Receiving attention in a recent systematic review, CDT has been shown to have acceptable reproducibility even with the use of different devices (Geber et al., 2011; Moloney, Hall, & Doody, 2012; Zinman, Bril, & Perkins, 2004). In addition, CDT has demonstrated excellent performance characteristics in identifying DSP in people with type 1 diabetes (Lysy et al., 2014). We aimed to validate the findings observed in type 1 diabetes by systematically evaluating CDT as a marker of DSP in a cross-sectional type 2 diabetes cohort, and aimed to compare it to other small fiber functional measures and clinical scores.

2. Materials and Methods

Two hundred and fifty-one patients with type 2 diabetes from the Diabetes and Endocrinology Clinic and the Diabetic Neuropathy Clinic at the Toronto General Hospital were accrued for an ongoing study initially funded by the Canadian Diabetes Association (CDA Grant# OG-3-10-3123-BP); of these, 220 had CDT measurements. Each participant completed a neuropathy assessment between November 2010 and May 2013. The assessments included a comprehensive medical and neurological evaluation, past medical history, biochemical tests, nerve conduction studies (NCS) and small and large fiber function tests. The 31 participants who did not receive CDT did not significantly differ in clinical and biochemical characteristics from those that did. All participants provided written informed consent. The protocol and consent procedures were conducted in accordance with the World Medical Association's Helsinki Declaration and were approved by the Multidisciplinary Research Ethics Board of the Toronto General Hospital Research Institute.

2.1. Selection and characteristics of type 2 participants

Participants were included if they had a physician-reported diagnosis of type 2 diabetes based on Canadian Diabetes Association Guidelines (Goldenberg & Punthakee, 2013), were aged ≥18 years, provided informed consent, and did not have neuropathy attributable to causes other than diabetes. These causes were excluded by detailed medical history, family history of neuropathy, history of toxin exposure, renal failure, or presence of abnormal serum or urine protein electrophoresis. Comprehensive medical examinations of each participant were also performed alongside the neurological evaluation to determine clinical characteristics. These involved assessment of neuropathy related symptoms and signs (blood pressure, heart rate), lifestyle factors (including smoking, alcohol history) and comorbidities. Presence of other diabetes complications such as retinopathy, nephropathy and macrovascular complications was determined by examination of the medical record or by participant self-report. Participants were also instructed to complete biochemical tests (including glycated hemoglobin A1C, cholesterol, kidney function tests and lipid profile) within 1 week of their medical and neurological examination. The study accrual strategy used a clinical stratification method to ensure representation of a broad spectrum of nerve injury, from no objective evidence of nerve injury, to severe neuropathy. This strategy used the Toronto Clinical Neuropathy Score (TCNS), a validated grading system that uses elements of the history and physical examination for assessing neuropathy severity (Bril & Perkins, 2002), and this strategy was used as a countermeasure to spectrum bias.

2.2. Classification of DSP case and control subjects

DSP was established using consensus criteria (England et al., 2005; Tesfaye et al., 2010) that called for the presence of clinical and electrophysiological abnormalities. We defined electrophysiological abnormality according to the presence of at least one abnormal nerve conduction parameter in both the sural sensory nerve and peroneal motor nerve as determined by the Counterpoint instrument (Natus Medical Incorporated, San Carlos, CA) (England et al., 2009). Measured NCS parameters included sural nerve amplitude potential and conduction velocity, and peroneal nerve amplitude potential, conduction velocity and F-wave latency, and they were scored as normal or abnormal according to age- and height-adjusted laboratory reference values (Oh, 2003). We defined clinical abnormality by the presence of ≥1 neuropathic sign and/or symptom, in keeping with a distal symmetrical neuropathic pattern of onset and progression (Shin, Bril, Orszag, Ahmed, & Perkins, 2011). Neuropathic signs and symptoms were assessed by a comprehensive medical and neurologic evaluation on each participant, and symptoms included numbness, tingling, weakness, foot pain, and ataxia, while signs included abnormal knee or ankle reflexes, temperature, light touch, monofilament, and vibration sensation. Severity of DSP was assessed according to the total number of abnormal NCS parameters present (out of 5), with those having a greater number of abnormalities judged as having a higher degree of neuropathy. We defined an exploratory "preclinical DSP" as a way of classifying early-stage DSP: preclinical DSP cases were defined as those who did not meet the clinical DSP case criteria, but presented with at least one abnormal NCS parameter, regardless of signs and symptoms (Lysy et al., 2014). Controls were people with diabetes but without neuropathy and defined by the absence of any abnormal electrophysiological parameter.

2.3. Assessment of small nerve fiber function

Quantitative sensory measurement using CDT was obtained with the TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat-Yishai, Israel). CDT is a measure of thermosensory spinal afferents. Using the method of limits (Levy, Abraham, & Reid, 1989), a stimulator was applied to the dorsum of the foot (L5 dermatome) at a temperature of 32 °C and gradually decreased at a rate of 1 °C per second to the first level detected by the patient as cooler than the preceding level. Participants depressed a button when they perceived the cooling sensation and the sensory threshold was recorded. The test was performed five times bilaterally on the great toe. The five trials from each foot were averaged to establish a mean CDT; a catch trial involving a null stimulus was inserted between the five trails at random to ensure patient understanding of the procedure. Age- and gender-adjusted Z-scores for CDT were generated using the formula

$$Z = \left(X_{single\ patient} - Mean_{controls}\right) / SD_{controls}$$ (Rolke et al., 2006; Yarnitsky & Sprecher, 1994).

Axon reflex–mediated neurogenic vasodilatation in response to cutaneous heating by the laser Doppler imaging flare technique (LDI_{FLARE}) was measured using the moorLDI2 (Moor Instruments Ltd., Axminster, U.K.). LDI_{FLARE} is a measure of nociceptive spinal afferents. A 44 °C heating probe was applied to the skin on the dorsum of the right foot for 20 min. Blood flow in the dermal capillaries was measured over a 6 × 6 cm area using MoorLDI software (version 3.11) (Krishnan & Rayman, 2004) and the LDI_{FLARE} area was calculated in centimeters squared.

Heart rate variability (HRV) was assessed by RR interval variation, by using the Dantec Keypoint Workstation (Natus Medical Inc., San Carlos, CA), according to a defined protocol described elsewhere (Stalberg & Nogues, 1989). HRV is a measure of parasympathetic vagal