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Better diagnostic accuracy of neuropathy in obesity: A new challenge for neurologists

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HIGHLIGHTS

- Specific combinations of neuropathy measures should be used to maximize performance in obese cohorts.
- More neuropathy measures have good test characteristics for distal symmetric polyneuropathy than for small fiber neuropathy or cardiovascular autonomic neuropathy.
- Large fiber measures are more highly correlated than small fiber measures.

ABSTRACT

Objective: To determine the comparative diagnostic characteristics of neuropathy measures in an obese population.
Methods: We recruited obese participants from the University of Michigan's Weight Management Program. Receiver operative characteristic analysis determined the area under the curve (AUC) of neuropathy measures for distal symmetric polyneuropathy (DSP), small fiber neuropathy (SFN), and cardiovascular autonomic neuropathy (CAN). The best test combinations were determined using stepwise and Score subset selection models.
Results: We enrolled 120 obese participants. For DSP, seven of 42 neuropathy measures (Utah Early Neuropathy Score (UENS, N = 62), Michigan Neuropathy Screening Instrument (MNSI) reduced combined index, MNSI examination, nerve fiber density (NFD) leg, tibial F response, MNSI questionnaire, peroneal distal motor latency) had AUCs $\geq$ 0.75. Three of 19 small fiber nerve measures for SFN (UENS, NFD leg, Sudoscan feet (N = 70)) and zero of 16 CAN measures had AUCs $\geq$ 0.75. Combinations of tests performed better than individual tests with AUCs of 0.82 for DSP (two parameters) and 0.84 for SFN (three parameters).
Conclusions: Many neuropathy measures demonstrate good test performance for DSP in obese participants. Select few small fiber nerve measures performed well for SFN, and none for CAN.
Significance: Specific combinations of tests should be used for research studies to maximize diagnostic performance in obese cohorts.
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1. Introduction

Globally, the prevalence of overweight and obesity has increased by more than 27% over the last 33 years (Ng et al., 2014). Given this worldwide epidemic and the association between obesity and peripheral neuropathy, there is a need to investigate the diagnostic characteristics of neuropathy measures in obese populations (Tesfaye et al., 2005; Van Acker et al., 2009). It is well documented that neuropathy measures are susceptible

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to the effects of age, height, and temperature (Denys, 1991; Rivner et al., 2001), yet few studies to date have examined the effect of body habitus, and none comparing a comprehensive list of neuropathy measures in an obese population. This is a critical point because obesity is a potential confounding factor in the quantitative assessments of neuropathy (Boyraz and Saracoglu, 2010).

Obese patients can develop multiple types of peripheral neuropathy including distal symmetric polyneuropathy (DSP), small fiber neuropathy (SFN), and cardiovascular autonomic neuropathy (CAN) (Callaghan et al., 2012, 2015). Many neuropathy measures exist to evaluate each of these conditions, but few studies compare these measures and none have focused on obese populations. Furthermore, past studies often report sensitivity and specificity without reporting the area under the curve (AUC) to allow direct comparisons between tests (McArthur et al., 1998; Baraz et al., 2014). Therefore, further information is needed regarding the comparative performance of neuropathy tests, as well as the best combinations of these tests, for the most common subtypes of neuropathy in obese populations.

In the current study, we performed extensive neuropathy testing in a cohort of obese participants. We aimed to determine the diagnostic characteristics of neuropathy measures, including combinations of tests, utilizing a clinical definition of DSP regardless of the underlying cause of neuropathy. Furthermore, we studied the test performance of small fiber neuropathy measures for SFN and CAN among our obese participants, and investigated the correlation between large fiber measures and separately between small fiber measures. This is the first report of the comparative diagnostic characteristics of comprehensive neuropathy measures for the most common subtypes of peripheral neuropathy in a well-characterized, obese population. As the obesity prevalence continues to increase worldwide, the importance of choosing the best neuropathy measures in this population will also continue to rise.

2. Materials and methods

2.1. Population

We recruited obese patients attending the University of Michigan Weight Management Program (prior to starting a diet/exercise regimen) from November 2010 to December 2015 as previously described (Callaghan et al., 2016). Briefly, participants were required to have a body mass index (BMI) $\geq$ 35 kg/m^2 or $\geq$32 kg/m^2 if they had one or more medical condition in addition to obesity (Rothberg et al., 2015). Of note, neuropathy was not considered as a medical condition for inclusion. Participants were excluded if they were on anticoagulant medications since these therapies increase the risks associated with skin biopsy.

This study was approved by the University of Michigan Institutional Review Board, and all participants signed an informed consent.

2.2. Primary outcome-DSP

Clinical DSP was defined according to the Toronto consensus definition of probable polyneuropathy, which requires 2 or more of the following: neuropathy symptoms, abnormal sensory examination, and abnormal reflexes (Dyck et al., 2011). Of note, a clinical definition of neuropathy provides sufficient accuracy for use in epidemiologic studies and clinical practice (England et al., 2005; Pop-Busui et al., 2017). One of four board certified neuromuscular specialists performed a standardized history and examination to determine these criteria.

2.3. Secondary outcome-SFN

Clinical SFN was defined according to the Toronto consensus definition of probable SFN, which requires neuropathic symptoms and an abnormal small fiber sensory examination (based on pinprick sensation) (Malik et al., 2011).

2.4. Secondary outcome-CAN

CAN was defined as an abnormality on one or more of four cardiovascular reflex tests (expiration to inspiration (E:I) ratio, 30:15 ratio, the average of two Valsalva ratios, and orthostatic hypotension defined as a systolic blood pressure drop of more than 20 or a diastolic blood pressure drop of more than 10). This definition was chosen because autonomic symptoms do not correlate with autonomic measures (Low et al., 2004; Pop-Busui et al., 2009), which precludes use of a comparable clinical definition of autonomic neuropathy. Furthermore, cardiovascular reflex tests are associated with mortality (Maser et al., 2003) and are considered the gold standard definition of autonomic neuropathy (Spallone et al., 2011). Lean controls from a recent study were used to determine 5th percentile cutoffs for the first three cardiovascular reflex tests (Callaghan et al., 2016).

2.5. Measures of large fiber nerve injury

Nerve conduction studies were performed by a certified nerve conduction study technologist using the CareFusion's Viking on Nicolet EDX electrodiagnostic system. A total of six nerves (sural sensory, peroneal motor, tibial motor, ulnar sensory, median sensory, median motor) and 17 parameters were measured. Quantitative sensory testing (QST) measurements of vibration detection thresholds were performed using the WR Medical Electronics Co. Computer Aided Sensory Evaluator (CASE) IV. The CASE IV vibration stimulator was placed on the dorsum of the dominant great toe. The patient's vibration detection threshold was measured as the Just Noticeable Difference (JND). Monofilament testing was performed with a Semmes Weinstein 5.07/10-g monofilament on the dorsum of the dominant great toe. Monofilament testing was normal if the participant felt 8 or more out of 10 responses, reduced for 1–7 responses, and absent for zero responses. Neurothesiometer testing was performed using the Scientific Laboratory Supplies device on the plantar surface of the dominant great toe. The Neurothesiometer applies 0–50 V, which provides a corresponding vibration amplitude between 0 and 250 μm. Intensity was increased until it was reliably felt, and we used the average of three trials. The Michigan Neuropathy Screening Instrument (MNSI) questionnaire and examination (performed by a neuromuscular specialist) were performed as previously described (Feldman et al., 1994). We also calculated the MNSI reduced combined index, which utilizes the most predictive questionnaire and examination components, based on a previous study (Herman et al., 2012).

2.6. Measures of small fiber nerve injury

NFD was evaluated using brightfield immunohistochemistry. Fibers were labeled with rabbit anti-PGP 9.5 antibody and individual nerve fibers that cross into the epidermis were counted based on an established protocol (Lauria et al., 2010). The total fiber count was calculated by averaging the fibers in 4 sections of skin at each biopsy site (fibers per millimeter). NFD was measured at the distal leg (10 cm above the lateral malleolus) and proximal thigh (20 cm below the anterior superior iliac spine) of the patients left leg from a 3 mm skin biopsy (Callaghan et al., 2012). Quantitative sensory testing (QST) measurements