Can Ultrasound of the Tibial Nerve Detect Diabetic Peripheral Neuropathy?

A cross-sectional study

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OBJECTIVE—Peripheral nerve imaging by portable ultrasound (US) may serve as a noninvasive and lower-cost alternative to nerve conduction studies (NCS) for diagnosis and staging of diabetic sensorimotor polyneuropathy (DSP). We aimed to examine the association between the size of the posterior tibial nerve (PTN) and the presence and severity of DSP.

RESEARCH DESIGN AND METHODS—We performed a cross-sectional study of 98 consecutive diabetic patients classified by NCS as subjects with DSP or control subjects. Severity was determined using the Toronto Clinical Neuropathy Score. A masked expert sonographer measured the cross-sectional area (CSA) of the PTN at 1, 3, and 5 cm proximal to the medial malleolus.

RESULTS—Fifty-five patients had DSP. The mean CSA of the PTN in DSP compared with control subjects at distances of 1 (23.03 vs. 17.72 mm²; P = 0.004), 3 (22.59 vs. 17.69 mm²; P < 0.0001), and 5 cm (22.05 vs. 17.25 mm²; P = 0.0005) proximal to the medial malleolus was significantly larger. Although the area under the curve (AUC) for CSA measurements at all three anatomical levels was similar, the CSA measured at 3 cm above the medial malleolus had an optimal threshold value for identification of DSP (19.01 mm²) with a sensitivity of 0.69 and a specificity of 0.77 by AUC analysis.

CONCLUSIONS—This large study of diabetic patients confirms that the CSA of the PTN is larger in patients with DSP than in control subjects, and US is a promising point-of-care screening tool for DSP.

Ultrasound (US) for nerve imaging is increasingly used by various medical specialties for both diagnostic and therapeutic purposes (1,2). Modern US machines permit real-time, point-of-care imaging of nerves and their surrounding structures with high fidelity and without patient discomfort or radiation exposure. One promising application of US technology of interest to internists, anesthesiologists, and surgeons may be its ability to rapidly and reliably identify peripheral neuropathy, which traditionally requires resource-intensive nerve conduction studies (NCS) for formal diagnosis (3,4). Preliminary data signal a direct relationship that is independent of BMI, age, height, or weight between the presence of diabetic neuropathy and a greater cross-sectional area (CSA) of peripheral nerves as visualized by US (5,6). However, these previously published studies are limited by small sample sizes and cannot offer predictive values for US as a diagnostic test (6–8). In this larger observational study, we aimed to determine whether US can reliably detect the presence and severity of diabetic sensorimotor polyneuropathy (DSP). We hypothesized that the CSA of the posterior tibial nerve (PTN) as measured by US is higher in diabetic patients with DSP compared with diabetic patients without DSP.

RESEARCH DESIGN AND METHODS—The cross-sectional study was performed at the Toronto General Hospital, University Health Network (UHN), in 2011. The UHN research ethics board approved the study. Ninety-eight consecutive diabetic patients undergoing NCS evaluation for DSP at the Toronto General Hospital Electromyography laboratory were recruited to the study and provided written informed consent. Patients with type 1 diabetes for >5 years, and all patients with type 2 diabetes were included. Patients with polyneuropathy due to other etiological causes such as hereditary, alcoholic, metabolic, inflammatory, or toxic factors were excluded from participation in the study. Demographic information of age, sex, BMI, blood pressure, HbA1c, and type and duration of diabetes was recorded for all patients. A detailed neurologic history and examination was performed and the Toronto Clinical Neuropathy Score (TCNS) was recorded for all patients. Severity of DSP was determined by the TCNS score (out of 19 points so that 0–5, DSP absent; 6–11, mild-moderate DSP; and ≥12, severe DSP) (9).

All study patients underwent NCS and sonographic examination of the PTN at the same visit as described below.

NCS and classification of DSP subjects and control subjects

All NCS were performed in the electromyography laboratory at the Toronto General Hospital by experienced technologists and supervised by a neurologist (V.B.), using the Cadwell EMG equipment (Cadwell Laboratories Inc., Kennewick, WA) according to the standards of the American Association for Neuromuscular and Electrodiagnostic Medicine and the...
Diabetic neuropathy and ultrasound

Figure 1—Right panel: ankle position, and US probe placement at 1, 3, and 5 cm proximal to the cephalad border of the medial malleolus (*M). Left panel: short-axis image of the PTN above the medial malleolus. CSA is measured by multiplying the short (a) and long (b) axes of the PTN at each level (CSA = a × b × π × 1/4). TA, posterior tibial artery. (A high-quality color representation of this figure is available in the online issue.)

Canadian Society of Clinical Neurophysiology (10,11).

Recordings were performed with temperature control (32–34°C), fixed distance measurements, and recording of well-defined and artifact-free responses. The patients had unilateral nerve conduction testing of the peroneal and tibial motor nerves and the sural sensory nerve using standardized protocols. Latencies, distances, and amplitudes were measured using onset latencies and baseline-to-peak amplitudes for motor and sensory responses, excepting initial positive peak (if present) to negative peak for sensory potential amplitude measurements. F-waves were generated at the ankle for all motor nerves and the minimal reproducible latency used. Conduction velocities were calculated for both motor and sensory nerves.

The case definition for DSP was consistent with the clinical and electrophysiological criteria set forth by the American Association of Neurology, the American Academy of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (12). Clinical criteria required the presence of more than one symptom (numbness, tingling, weakness, foot pain, or ataxia) or sign (abnormal knee or ankle reflexes, temperature, light touch, monofilament, or vibration sensation), in keeping with a distal symmetrical neuropathic pattern of onset and progression. Electrophysiological abnormality was defined by at least one abnormal NCS parameter in both sural and peroneal nerve distributions assessed using the Cadwell EMG equipment (Cadwell Laboratories Inc.) with age- and height-adjusted thresholds for abnormality (13).

Sonographic examination of PTN
A standardized systematic ultrasound examination of the PTN was performed by a trained sonographer (S.A.) who was masked to the NCS results and patient category. Beginning proximal to the cephalad border of the medial malleolus, the PTN was imaged in the short axis and traced proximally using a Sonosite M-turbo ultrasound machine and HFL38X transducer (6–13 MHz) (Sonosite Inc, Bothell, WA). A short-axis image of the PTN was visualized, captured, and stored at each of three separate levels, specifically 1 cm, 3 cm, and 5 cm proximal to the cephalad border of the medial malleolus (Fig. 1). The CSA of the PTN was calculated by multiplying the short (a) and long (b) axes of the PTN at each of the three levels. The mean CSA area = CSA = a × b × π × 1/4 (14) was reported as mm² for each level.

Statistical analysis and sample size calculation
Analyses were performed in SAS (version 9.2 for Windows; SAS Institute).

Table 1—Patient characteristics, CSA measurements, and NCS results

| Clinical characteristic          | Subjects with DSP (n = 55) | Control subjects without DSP (n = 43) | P value |
|---------------------------------|---------------------------|--------------------------------------|---------|
| Age (years)                     | 61.4 ± 11.9               | 46.8 ± 17.1                          | <0.0001 |
| Female sex (%)                  | 15 (27.3)                 | 20 (46.5)                            | 0.049   |
| Type 1 DM (%)                   | 12 (21.8)                 | 25 (58.1)                            | —       |
| Type 2 DM (%)                   | 43 (78.2)                 | 18 (41.9)                            | 0.0002  |
| Diabetes duration (years)       | 17.2 ± 12.4               | 16.8 ± 10.9                          | NS      |
| BMI (kg/m²)                     | 28.5 ± 8.5                | 26.6 ± 6.5                           | NS      |
| Systolic blood pressure (mmHg)  | 142.5 ± 19.4              | 126.1 ± 17.2                         | 0.0002  |
| Diastolic blood pressure (mmHg) | 76.4 ± 8.8                | 72.4 ± 10.3                          | NS      |
| HbA1c (%)                       | 7.5 ± 1.3                 | 7.5 ± 1.0                            | NS      |
| TCN [median (IQR)]             | 10 (7–12)                 | 4 (2–9)                              | <0.0001 |
| Mean CSA at 1 cm (mm² ± SD)     | 23.03 ± 8.65              | 17.72 ± 6.49                         | 0.0004  |
| Mean CSA at 3 cm (mm² ± SD)     | 22.59 ± 7.00              | 17.69 ± 5.05                         | <0.0001 |
| Mean CSA at 5 cm (mm² ± SD)     | 22.05 ± 7.40              | 17.25 ± 4.68                         | 0.0005  |
| Nerve conduction studies        |                           |                                      |         |
| Posterior tibial nerve          |                           |                                      |         |
| Dista amplitude (mV)            | 5.0 ± 3.8                 | 11.5 ± 4.7                           | <0.0001 |
| Distal latency (ms)             | 4.6 ± 1.0                 | 3.9 ± 0.7                            | 0.0004  |
| F-wave latency (ms)             | 64.1 ± 6.3                | 52.6 ± 4.8                           | <0.0001 |
| Proximal amplitude (mV)         | 3.3 ± 2.8                 | 8.3 ± 3.5                            | <0.0001 |
| Proximal latency (ms)           | 14.9 ± 2.7                | 12.2 ± 1.9                           | <0.0001 |
| Conduction velocity (m/s)       | 39.4 ± 7.6                | 46.7 ± 3.4                           | <0.0001 |
| Sural nerve                     |                           |                                      |         |
| Amplitude (µV)                  | 3.3 ± 4.3                 | 10.8 ± 5.1                           | <0.0001 |
| Latency (ms)                    | 3.5 ± 0.4                 | 3.0 ± 0.2                            | <0.0001 |
| Conduction velocity (m/s)       | 38.0 ± 3.8                | 46.9 ± 3.5                           | <0.0001 |
| Peroneal nerve                  |                           |                                      |         |
| Distal amplitude (mV)           | 2.6 ± 1.8                 | 5.1 ± 2.0                            | <0.0001 |
| Distal latency (ms)             | 4.9 ± 1.0                 | 4.3 ± 0.8                            | 0.008   |
| Conduction velocity (m/s)       | 36.0 ± 5.4                | 43.1 ± 4.1                           | <0.0001 |
| F-wave latency (ms)             | 61.4 ± 6.3                | 52.0 ± 5.2                           | <0.0001 |

Data are presented as mean ± SD or as a proportion, unless otherwise indicated. P values were calculated using the t test for continuous variables and the χ² test for categorical variables, unless otherwise indicated. DM, diabetes mellitus; IQR, interquartile range. *P value calculated using Wilcoxon rank sum test.
Comparisons of demographic and electrophysiologic data between DSP subjects and control subjects were analyzed using the Student t test for continuous variables and the χ² test for categorical parametric variables. The Wilcoxon rank sum test was performed to compare nonparametric variables. Receiver operating characteristic (ROC) curve analyses were performed to determine the sensitivity and specificity of CSA for the diagnosis of DSP at different points proximal to the medial malleolus. Linear regression analyses were performed for CSA at 1, 3, and 5 cm proximal to the medial malleolus against DSP severity as determined by the TCNS. Multiple linear regression was performed to compare CSA and three tibial nerve variables of distal amplitude, latency, and F-wave latency. Logistic regression analyses, in which DSP was the dependent variable and CSA, age, and systolic blood pressure were the independent variables, were performed to identify potential confounding effects. P < 0.05 was considered significant.

Accrual was based on the sample size necessary to detect a difference of 6.1 mm² in CSA between subjects and control subjects, given a predicted SD of 1.19 mm² under the assumption that DSP subjects would have greater CSA (6). The number of DSP subjects required for a one-tailed z-score percentile was 38 patients.

**RESULTS**—Patient characteristics for the 98 study participants are presented in Table 1. Fifty-five patients had DSP, and 43 were control subjects. Patients with DSP were older males with higher systolic blood pressure. Current diabetes control and duration of diabetes did not differ between the groups. The NCS data for DSP subjects and control subjects are presented in Table 1. Compared with the control subjects, the DSP subjects demonstrated lower sensory nerve action potential amplitudes, slower motor and sensory nerve conduction velocities, and longer distal motor, sensory, and F-wave latencies.

The mean CSA of the PTN at 1 (23.03 ± 17.72 mm²; P = 0.004), 3 (22.59 ± 17.69 mm²; P < 0.001), and 5 cm (22.05 ± 17.25 mm²; P = 0.005) above the medial malleolus was significantly larger in the DSP subjects compared with the control subjects (Table 1). Linear regression analyses revealed an inverse relationship between CSA and distal tibial compound muscle action potential amplitude and between CSA and DSP severity (Table 2). Including additional tibial nerve parameters (distal motor latency, F-wave latency) did not change the results in a meaningful way. The association between distal amplitude of the tibial nerve and CSA was independent of both age and systolic blood pressure (Table 2).

The ROC curve analyses revealed similar areas under the ROCs for CSA at 1, 3, and 5 cm. Though the area under the curve (AUC) did not differ for CSA measurements at different anatomical levels, the CSA measured at 3 cm above the medial malleolus had an optimal threshold value for identification of DSP (19.01 mm²) with a sensitivity of 0.69 and a specificity of 0.77 by AUC analysis (Fig. 2).

**CONCLUSIONS**—This large study of diabetic patients is the first to demonstrate that the cross-sectional area of the PTN as measured by US is a valid and reliable tool to detect the presence and predict the severity of DSP. The strength and novelty of this study stem from its robust design, a large sample population, validated NCS protocol, and standardized sonographic imaging procedure.

DSP develops due to the metabolic derangements associated with chronic hyperglycemia, including increased polyol flux, accumulation of advanced glycation end products, oxidative stress, and lipid alterations that can cause axonal loss and other structural neural changes (15,16). Peripheral nerve swelling in the setting of DSP presumably stems from increased water content as a byproduct of the aldose reductase conversion process of glucose into sorbitol.
The sural nerve is one of the earliest nerves affected in diabetic neuropathy as a subclinical sensory nerve deficit on NCS (17) and is therefore routinely examined for diagnostic NCS purposes (18). The PTN at the ankle is comparable in length to the sural nerve and may be similarly affected in this length-dependent process. In light of the documented reliability of CSA measurements of the PTN at the level of the tarsal tunnel using high resolution US (19,20), the PTN is a reasonable choice as the subject of this investigation.

Modern ultrasonography for examination of nerves is attractive to a wide variety of medical practitioners due to its ease of use, portability, and efficiency, as well as the ability to image the entire length of a nerve in real-time (21). Reliable sonographic detection of DSP at the bedside is of particular interest to anesthesiologists who perform nerve blocks. Because there currently exists no reliable and practical method to determine the presence and/or severity of peripheral neuropathy preoperatively at the bedside, many diabetic patients with otherwise healthy nerves may receive general anesthesia instead of regional anesthesia, thus forfeiting some or all of the benefits associated with the latter technique, including a reduction in morbidity (25), superior postoperative analgesia (26), and enhanced cost effectiveness (27). In conclusion, this large study of diabetic patients confirms that the CSA of the PTN is larger in patients with DSP than in control subjects and that a threshold value of 19.01 mm² provides acceptable diagnostic characteristics to identify DSP with a sensitivity of 69% and specificity of 77%, corresponding to a threshold value of 19.01 mm².

Figure 2—ROC curve for the identification of DSP by PTN CSA at 1, 3, and 5 cm in 98 subjects. The curve depicting PTN CSA measured at 3 cm proximal to the cephalad border of the medial malleolus is represented by the solid black line. Its AUC of 0.731 was the largest among the three measurements taken. The point exhibiting the optimal operating characteristics, indicated by *, was on the curve for CSA at 3 cm; it had a sensitivity of 69% and a specificity of 77%, corresponding to a threshold value of 19.01 mm².
promising point-of-care screening tool to determine the presence of DSP.

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References

1. Boon AJ, Harper CM. Ultrasound in the diagnosis of mononeuropathy: future directions. Muscle Nerve 2011;44:851–853
2. Kopf H, Loizides A, Mostbeck GH, Gruber H. Diagnostic sonography of peripheral nerves: indications, examination techniques and pathological findings. Ultraschall Med 2011;32:242–263; quiz 264–266
3. Hooper DR, Lawson W, Smith L, Baker SK. Sonographic features in hereditary neuropathy with liability to pressure palsies. Muscle Nerve 2011;44:862–867
4. Lucchetta M, Pazzaglia C, Granata G, Briani C, Padua L. Ultrasound evaluation of peripheral neuropathy in POEMS syndrome. Muscle Nerve 2011;44:868–872
5. Cartwright MS, Passmore LV, Yoon J-S, Brown ME, Caress JB, Walker FO. Cross-sectional area reference values for nerve ultrasonography. Muscle Nerve 2008;37:566–571
6. Watanabe T, Ito H, Sekine A, et al. Sonographic evaluation of the peripheral nerve in diabetic patients: the relationship between nerve conduction studies, echo intensity, and cross-sectional area. J Ultrasound Med 2010;29:697–708
7. Lee D, Dauphinée DM. Morphological and functional changes in the diabetic peripheral nerve: using diagnostic ultrasound and neurosensory testing to select candidates for nerve decompression. J Am Podiatr Med Assoc 2005;95:433–437
8. Watanabe T, Ito H, Monta A, et al. Sonographic evaluation of the median nerve in diabetic patients: comparison with nerve conduction studies. J Ultrasound Med 2009;28:727–734
9. Bril V, Perkins BA. Validation of the Toronto Clinical Scoring System for diabetic polyneuropathy. Diabetes Care 2002;25:2048–2052
10. American Association of Electrodiagnostic Medicine. Guidelines in electrodiagnostic medicine. Recommended policy for electrodiagnostic medicine. Muscle Nerve Suppl 2009;109:S1–S105
11. Bolton CF, Benstead TJ, Grand M, Fasion S, Tardif GS, Weston LE. Minimum standards for electromyography in Canada: a statement of the Canadian Society of Clinical Neurophysiologists. Can J Neurol Sci 2000;27:288–291
12. England JD, Gronseth GS, Franklin G, et al.; American Academy of Neurology; American Association of Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005;64:199–207
13. Oh S. Normal values for common nerve conduction tests. In Clinical Electromyography: Nerve Conduction Studies. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins, 2003, p. 86–100
14. Yesildag A, Kutluhan S, Sengul N, et al. The role of ultrasonographic measurements of the median nerve in the diagnosis of carpal tunnel syndrome. Clin Radiol 2004;59:910–915
15. Dyck PJ, Davies JL, Clark VM, et al. Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. Diabetes Care 2006;29:2282–2288
16. Tesfaye S, Chaturvedi N, Eaton SE, et al.; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. N Engl J Med 2003;352:341–350
17. Perkins BA, Bril V. Diabetic neuropathy: a review emphasizing diagnostic methods. Clin Neurophysiol 2003;114:1167–1175
18. Arezzo JC. The use of electrophysiology for the assessment of diabetic neuropathy. Neurosci Res Commun 1997;21:13–23
19. Fantino O, Coillard J-Y, Borne J, Bordet B. [Ultrasonography of the tarsal tunnel: Normal and pathological imaging features]. J Radiol 2011;92:1072–1080
20. Alshami AM, Cairns CW, Wyle BK, Souvils T, Coppeters MW. Reliability and size of the measurement error when determining the cross-sectional area of the tibial nerve at the tarsal tunnel with ultrasonography. Ultrasound Med Biol 2009;35:1098–1102
21. Smith J, Finnoff JT. Diagnostic and interventional musculoskeletal ultrasound—part 2. Clinical applications. PM R 2009;1:162–177
22. Moghtaderi A, Izadi S. Double crush syndrome: an analysis of age, gender and body mass index. Clin Neurol Neurosurg 2008;110:25–29
23. Akyuz M, Yalcin E, Selcuk B, Onder B, Ozçakar L. Electromyography and ultrasonography in the diagnosis of a rare double crush ulnar nerve injury. Arch Phys Med Rehabil 2011;92:1914–1916
24. Burgher AH, Hebl JR. Minimally invasive retrieval of knotted nonstimulating peripheral nerve catheters. Reg Anesth Pain Med 2007;32:162–166
25. Urwin SC, Parker MJ, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. Br J Anaesth 2000;84:450–455
26. Hadzic A, Arliass K, Kerimoglu B, et al. A comparison of intrafascicular nerve block versus general anesthesia for hand and wrist day-case surgeries. Anesthesiology 2004;101:127–132
27. Chan VW, Peng PW, Krasz Z, et al. A comparative study of general anesthesia, intravenous regional anesthesia, and axillary block for outpatient hand surgery: clinical outcome and cost analysis. Anesth Analg 2001;93:1181–1184
28. Ragi M, Van Acker N, Knaepen MWM, et al. Asymptomatic small fiber neuropathy in diabetes mellitus: investigations with intraepidermal nerve fiber density, quantitative sensory testing and laser-evoked potentials. J Neurol 2011;258:1852–1864