

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.

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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, HbA_{1c}, 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

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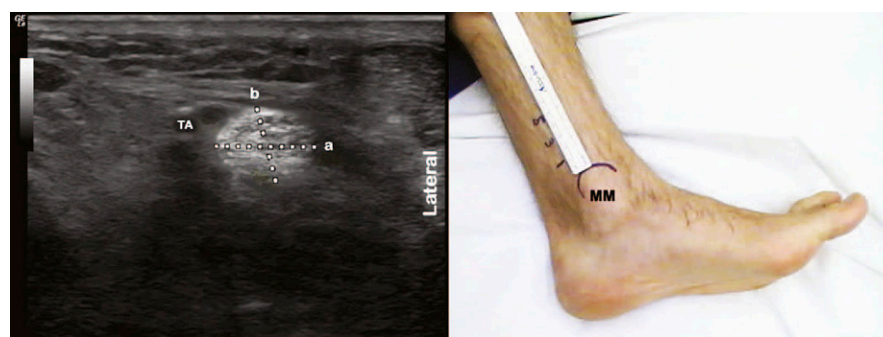


Figure 1—Right panel: ankle position, and US probe placement at 1, 3, and 5 cm proximal to the cephalad border of the medial malleolus (MM). Left panel: short-axis image of the PTN above medial malleolus. CSA is measured by multiplying the short (a) and long (b) axes of the PTN at each level ($CSA = a \times b \times \pi \times 1/4$). 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 ($= a \times b \times \pi \times 1/4$) (14) was reported as mm^2 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/m^2)	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
HbA _{1c} (%)	7.5 ± 1.3	7.5 ± 1.0	NS
TCNS [median (IQR)]	10 (7–12)	4 (2–9)	<0.0001*
Mean CSA at 1 cm ($mm^2 \pm SD$)	23.03 ± 8.65	17.72 ± 6.49	0.0004*
Mean CSA at 3 cm ($mm^2 \pm SD$)	22.59 ± 7.00	17.69 ± 5.05	<0.0001*
Mean CSA at 5 cm ($mm^2 \pm SD$)	22.05 ± 7.40	17.25 ± 4.68	0.0005*
Nerve conduction studies			
Posterior tibial nerve			
Distal 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 χ^2 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 χ^2 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 and compound muscle 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 vs. 17.72 mm²; $P = 0.0004$), 3 (22.59 vs. 17.69 mm²; $P < 0.0001$), and 5 cm (22.05 vs. 17.25 mm²; $P = 0.0005$) 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

Table 2—Regression results

	β (95% CI)	R ²	P value	Age-adjusted P value
Distal amplitude of the tibial nerve vs. CSA*				
CSA at 1 cm	−0.30 (−0.41 to −0.18)	0.21	<0.001	0.004
CSA at 3 cm	−0.37 (−0.51 to −0.22)	0.21	<0.001	0.003
CSA at 5 cm	−0.33 (−0.48 to −0.19)	0.18	<0.001	<0.001
TCNS score vs. CSA†				
CSA at 1 cm	0.24 (0.13–0.35)	0.17	<0.001	0.010
CSA at 3 cm	0.29 (0.16–0.42)	0.17	<0.001	0.010
CSA at 5 cm	0.21 (0.07–0.34)	0.09	0.004	0.090
Number of abnormal NCS parameters vs. CSA‡				
CSA at 1 cm	0.14 (0.07–0.20)	0.16	<0.001	0.020
CSA at 3 cm	0.19 (0.11–0.26)	0.20	<0.001	0.002
CSA at 5 cm	0.17 (0.09–0.24)	0.16	<0.001	0.002
DSP severity vs. CSA§				
CSA at 1 cm	0.04 (0.02–0.05)	0.15	<0.001	0.010
CSA at 3 cm	0.05 (0.03–0.07)	0.17	<0.001	0.005
CSA at 5 cm	0.04 (0.02–0.06)	0.13	<0.001	0.006

P values from testing the hypothesis that the slope parameter β differs from zero. * β measures the associated change in distal amplitude (measured in mV) per unit increase in CSA (measured in mm²). † β measures the associated change in TCNS score per unit increase in CSA (measured in mm²). ‡ β measures the associated change in the number of abnormal nerve conduction parameters presented per unit increase in CSA (measured in mm²). §DSP severity is based on the TCNS score, with a score of 0–5 indicating no neuropathy, 6–11 indicating mild to moderate neuropathy, and ≥ 12 indicating severe neuropathy. For DSP severity, β measures the associated change in group status, moving from a milder severity of DSP to a stronger one, per unit increase in CSA (measured in mm²).

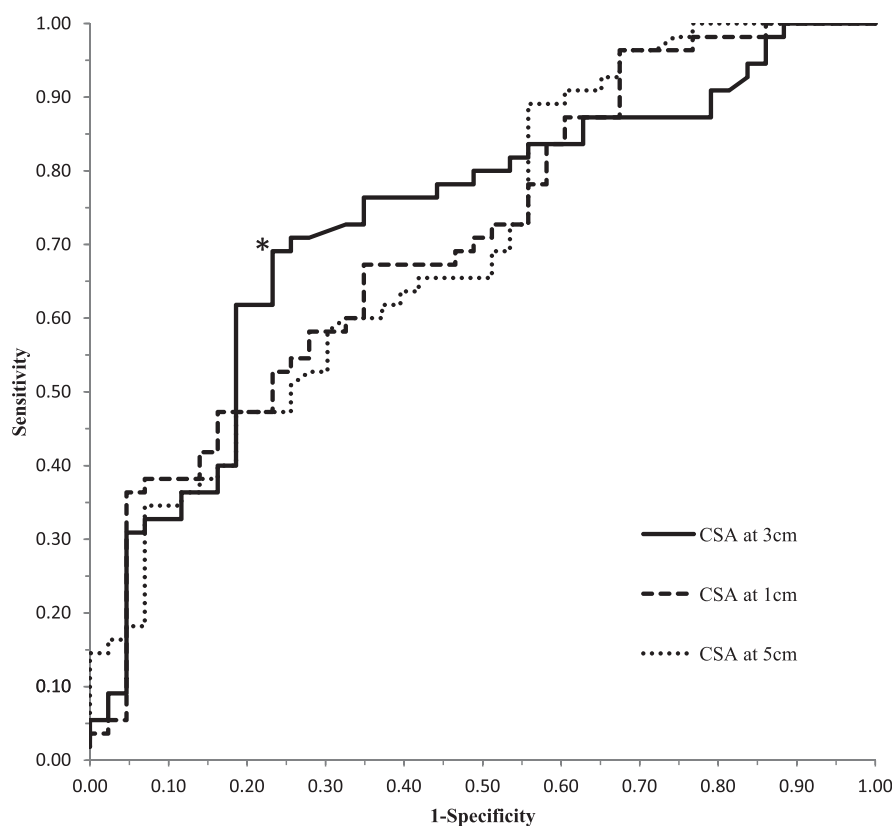


Figure 2—ROC curve for the identification of DSP by PTN CSA at 1, 3, and 5 cm in 98 subjects. The curve depicting PTN CSA measured at 3 cm proximal to the cephalad border of the medial malleolus is represented by the solid black line. Its AUC of 0.731 was the largest among the three measurements taken. 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.

(7). 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. Although no study explicitly recommends avoiding peripheral nerve blocks in diabetic patients with peripheral neuropathy, there remains underlying uncertainty regarding the preferred technique

and the likelihood of block-related nerve damage. Needle trauma and local anesthetic injection around a nerve that is already compromised may pose additional risk of further neurologic injury because of a physiologic “double-crush” (22,23). Hebl and colleagues (24) suggested avoidance of epinephrine in local anesthetic solutions used in diabetic patients. 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). The second phase of this study, which is now underway, investigates the association between the CSA of the PTN and the occurrence of clinical or subclinical nerve damage following a local anesthetic nerve block of the PTN in diabetic patients with DSP (clinical trial registry

number NCT01002053, clinicaltrials.gov). If nerve CSA is ultimately shown to be a predictor of block-related nerve damage, then this bedside test will provide evidence-based guidance to those considering nerve blocks in patients with DSP.

There are several limitations associated with our study. Our findings may not be generalizable to other types of peripheral neuropathy having different pathophysiology. In addition, despite being the current gold standard for the diagnosis and assessment of severity of DSP, NCS may not be sensitive enough to detect minor degrees of peripheral nerve impairments early in the course of neuropathy (28). However, it is unlikely that CSA would be more sensitive than NCS to confirm the diagnosis of DSP.

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 0.69 and specificity of 0.77. Consequently, US is a

promising point-of-care screening tool to determine the presence of DSP.

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S.R. researched data, contributed to the discussion, and wrote the manuscript. V.B., B.A.P., V.W.S.C., and H.E.-B. contributed to the discussion and reviewed and edited the manuscript. S.A., M.N., and L.E.L. researched data. R.B. researched data, contributed to the discussion, and reviewed and edited the manuscript. S.R. and R.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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