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ULTRASOUND

Diagnostic performance of two-dimensional shear wave elastography for evaluating tibial nerve stiffness in patients with diabetic peripheral neuropathy

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Abstract

Objectives To evaluate the stiffness of the tibial nerve with two-dimensional shear wave elastography (2D-SWE) and to determine whether 2D-SWE can be used to diagnose diabetic peripheral neuropathy (DPN).

Methods The study included 70 consecutive diabetic patients with DPN or without DPN and 20 healthy volunteers. The tibial nerve stiffness measured with 2D-SWE was studied. The differences in stiffness values among patients with DPN, patients with clinically defined DPN, patients without DPN, and healthy volunteers based on clinical features and electrodiagnostic tests were evaluated with the Mann–Whitney *U* test and the Kruskal–Wallis test. Inter- and intraobserver variability was evaluated, and a receiver operator characteristic curve analysis was performed.

Results The tibial nerve stiffness based on mean (E_{Mean}), minimum (E_{Min}), and maximum (E_{Max}) shear elasticity indices was significantly higher in patients with DPN and clinically defined DPN than that in patients without DPN and control subjects ($p < 0.05$). The area under the curve (AUC) for the SWE measurements of E_{Mean}, E_{Min}, and E_{Max} was 0.846, 0.867, and 0.821, respectively. An E_{Min} cutoff value of 45.7 kPa had a sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 74.0%, 87.6%, 6.0, and 0.3, respectively. The inter- and intraobserver agreements were excellent for the SWE measurements.

Conclusions Tibial nerve stiffness is significantly higher in diabetic patients with DPN and clinically defined DPN. The E_{Mean} and E_{Min} have a good accuracy for identifying DPN. Minor degree of peripheral nerve lesions appear to might exist in patients with clinically defined DPN, not detectable by electrophysiology. 2D-SWE has a potential use for cases with clinically defined DPN and can be detected with 2D-SWE.

Key Points

- *2D-SWE elastography is a noninvasive method that can be used to evaluate precise nerve stiffness for diagnosing DPN.*
- *Minor degree of neurologic lesion might exist early in patients with clinically defined DPN and can be detected by 2D-SWE.*
- *E_{Min} and E_{Mean} of SWE elasticity indices have better diagnostic accuracies than E_{Max} for identifying DPN.*

Keywords Diabetic neuropathies · Tibial nerve · Elasticity imaging techniques

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Abbreviations

2D-SWE	Two-dimensional shear wave elastography
AUC	Area under the curve
CSA	Cross-sectional area
DPN	Diabetic peripheral neuropathy
ICC	Intraclass correlation coefficient
LR(−)	Negative likelihood ratio
LR(+)	Positive likelihood ratio
NCS	Nerve conduction study
ROC	Receiver operator characteristic
ROI	Region of interest

Introduction

The diagnosis of diabetic peripheral neuropathy (DPN) is based on symptoms and clinical examinations and usually confirmed by electrophysiological tests [1–3]. Nerve conduction study (NCS) is considered the most feasible method for the diagnosis of DPN; however, this technique is limited by its invasiveness, cost, and discomfort [4, 5]. However, it is very common to encounter diabetic patients with abnormal clinical features but normal NCS results, which is known as "clinically defined DPN [6]."

Ultrasound (US) for nerve imaging is increasingly used as a complementary method to NCS, especially for evaluating the morphology of peripheral nerves, such as focal nerve entrapments [7, 8]. Previous studies [9–12] have reported the potential role of high-resolution ultrasound for the diagnosis of DPN, based on enlarged maximum thickness and cross-sectional area (CSA) of the tibial nerve. Nevertheless, the wide range of cutoff values and limited diagnostic accuracy may restrict its conclusiveness. Ultrasound elastography has recently emerged as a noninvasive tool for the evaluation of nerve stiffness [7, 13–15]. In a recent study [16], stiffness of the tibial nerve as evaluated with two-dimensional shear wave elastography (2D-SWE) was found to be much greater in diabetic patients with DPN than in patients without DPN and healthy individuals. In addition, a slightly increased nerve stiffness was observed in diabetic patients without DPN compared to that in healthy individuals. We hypothesize that peripheral nerve damage occurs in diabetic patients with clinically defined DPN and in patients with DPN and can be detected with 2D-SWE elastography. For this purpose, we evaluated tibial nerve stiffness with 2D-SWE elastography.

Materials and methods

This prospective study was performed at The Second Affiliated Hospital of Chongqing Medical University in the Department of Ultrasound. The local ethics committee of the hospital approved the study, and written informed consent was obtained from all volunteers and patients.

Seventy patients (25 males/45 females) with type 2 diabetes mellitus undergoing NCS evaluation and 20 volunteers (10 males/10 females) were recruited consecutively at the Second Affiliated Hospital of Chongqing Medical University from November 2017 to May 2018. Both ankles of 70 patients and 20 volunteers were examined by ultrasonography and 2D-SWE. All diabetic patients underwent NCS to assess neuropathy and were divided into three groups according to the presence or absence of DPN. Group A consisted of 25 patients with clinical signs or symptoms of DPN, confirmed by abnormal NCS. Group B consisted of 25 patients with clinical signs or symptoms of DPN but normal NCS. Group C consisted of 20 patients without clinical signs or symptoms of DPN and with normal electrophysiological testing. The control group consisted of 20 healthy volunteers with similar ages who had no history of diabetes or clinical signs or symptoms of DPN. Electrodiagnostic tests were not conducted in healthy volunteers. Demographic information including sex, age, weight, height, body mass index, blood pressure, HbA1c levels, and duration of diabetes were recorded for all patients. Type 2 diabetes mellitus was diagnosed by using the World Health Organization (WHO) criteria, which include a fasting plasma glucose level of at least 126 mg/dL (7.0 mmol/L) and a 2-h postprandial plasma glucose level of at least 200 mg/dL (11.1 mmol/L). The clinical criteria for DPN included the following: more than one symptom (foot pain, weakness, numbness, tingling, or ataxia) or sign (abnormal knee or ankle reflexes, temperature, light touch, monofilament, or vibration sensation). Patients with a known history of leg fractures or polyneuropathy due to other causes, such as hereditary, alcoholic, metabolic, or inflammatory, or with thyroid disorders were excluded. Patients with lesions identified on ultrasound examination of the ankle were excluded.

Electrophysiologic examinations

Routine NCS was conducted with a conventional procedure on a standard electromyography system (NeuroCare-C; Nuocheng Corporation). Recordings were performed with temperature control (32–34 °C), fixed distance measurements, and recording of well-defined and artifact-free responses. Every patient had bilateral nerve conduction testing of the peroneal and tibial motor nerves and the sural sensory nerve. Routine parameters, such as latencies, amplitudes, and conduction velocity, were obtained and recorded. All NCSs were conducted in the electromyography laboratory at The Second Affiliated Hospital of Chongqing Medical University by an experienced technologist (Weiwei Xu). The case definition for DPN was consistent with electrophysiologic criteria set by the American Association of Neurology, the American Academy of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation: at least one abnormal NCS parameter involving both the sural and peroneal nerves [17].

Patient positioning

All sonographic examinations were performed by two experienced sonographers (Weixi Jiang, Qunxia Zhang) who were blinded to the participants' history and NCS results in a quiet and temperature-controlled room. A commercially available device (Aixplorer; SuperSonic Imagine) with a 15–4-MHz linear array probe was used for sonographic examinations and SWE measurements while the subjects were lying in the supine position. Care was taken to perform the exams in slight plantar flexion with slight external rotation, with the lower extremity in a neutral position, avoiding any ankle movement, which may increase ankle soft tissue pressure.

SWE measurements

The transducer was placed on the skin surface with light contact using ample coupling gel to avoid compression effect, and the transducer remained stationary during acquisitions. The tibial nerve 4 cm proximal to the medial malleolus was identified in a transverse imaging plane, and then, the transducer was rotated 90° to view a sagittal imaging plane. Anatomic landmarks, such as the flexor digitorum longus and the posterior tibial vessels, were used to confirm the position of the tibial nerve. A short-axis image of the tibial nerve was captured 4 cm proximal to the cephalad border of the medial malleolus. Measurement of Young's modulus of the tibial nerve was obtained on sagittal imaging. The integrated SWE software allowed for placement of a circular regions of interest (ROI) of 2 mm within the elastography window and displayed the mean (E_{Mean}), minimum (E_{Min}), and maximum (E_{Max}) SWE elasticity indices (in kilopascals, kPa) within the ROI. Four iterative SWE measurements were performed with 2–3-min intervals. The mean, maximum, and minimum SWE elasticity values within each ROI were obtained by calculating the mean of four SWE measurements in each ankle.

Figure 1 shows an imaging procedure for SWE measurements of the tibial nerve 4 cm proximal to the cephalad border of the medial malleolus.

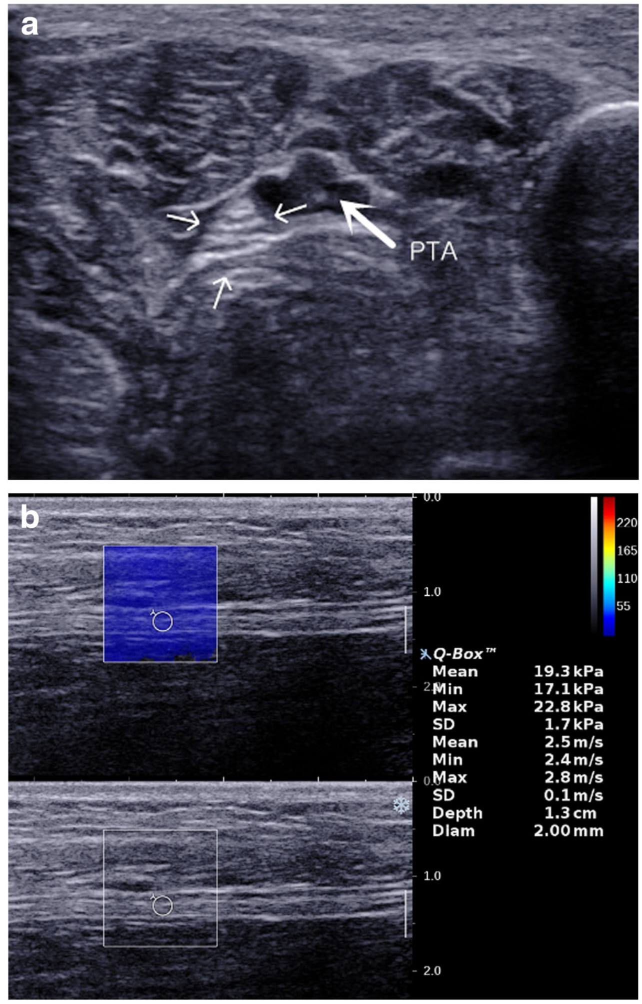

Fig. 1 **a** Transverse ultrasonography of the tibial nerve (thin arrow) 4 cm proximal to medial malleolar level in a 42-year-old male diabetic patient with DPN. PTA, posterior tibial artery. **b** Longitudinal split images of tibial nerve (between arrows) 4 cm proximal to medial malleolar levels in a 63-year-old male diabetic patient without DPN. Lower image is a longitudinal ultrasonography of tibial nerve with superimposed color box borders for SWE map and circular ROI for quantitative measurements on upper image. The E_{Mean}, E_{Min}, and E_{Max} elasticity indices are measured as 19.3, 17.1, and 22.8 kPa, respectively

Inter- and intraobserver diagnostic consistency calculation

The first sonographer (Weixi Jiang, with > 3 years' experience in sonography and elastography) examined all the study groups (70 patients and 20 volunteers) using conventional sonography and 2D-SWE. Then, 38 patients and 7 volunteers were selected to assess intraobserver variability using the block randomization method so that the first sonographer reexamined the patients within 24 h after the initial examination. A second sonographer (Qunxia Zhang, with > 10 years' experience in sonography and with > 3 years' experience in elastography) examined the same patients (38 patients and 7 volunteers) to assess interobserver variability within 24 h after the initial examination. Both sonographers were blinded to each other's evaluations and to the patients' and healthy subjects' other relevant examination results.

Statistical analyses

Statistical analyses were performed with SPSS software version 16.0 and MedCalc Statistical Software version 15.8. Continuous variables were expressed as the mean ± standard deviation. The average initial measurements obtained by the first examiner were analyzed for tibial nerve stiffness. The normal distribution of interclass data was tested with the Shapiro–Wilk test. Student's *t* test and *F* test for continuous variables were used to compare variables with a normal distribution. The Kruskal–Wallis test and Mann–Whitney *U* test were used to compare nonparametric variables among the four groups and between every two groups, respectively. The Wilcoxon signed-rank test was used to compare nerve stiffness between right and left sides. Correlations between elasticity indices and associated parameters were expressed by Spearman's correlation coefficient. A receiver operator characteristic curve (ROC) was generated by using the pooled average data (including measurements from the right and left sides), and we calculated the area under the curve (AUC) for E_{Mean}, E_{Min}, and E_{Max}. Optimal cutoff values for the tibial nerve elastic modulus were established by maximizing Youden's index on the ROC. The sensitivity (SE), specificity (SP), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) based on the optimal cutoff values were calculated. The AUC of E_{Mean}, E_{Min}, and E_{Max} were compared using *Z* test. The inter- and intraobserver agreements for nerve stiffness were evaluated by applying the interclass correlation coefficient (ICC) from a two-way random effects model analysis. Statistical significance was accepted at a $p < 0.05$. The inter- and intraobserver data were only used for inter- and intraobserver diagnostic consistency calculation.

Results

A total of 140 ankles of 70 patients and 40 ankles of 20 healthy volunteers were included in this study. The patient characteristics are presented in Table 1. Statistical analysis revealed that weight, body mass index, systolic blood pressure, diastolic blood pressure, and HbA1c levels were not significantly different among the study groups. Patients in group A were significantly older than those in group C (mean, 66.2 years vs 57.1 years; $p = 0.011$). Age was not significantly different among groups B and C and the control group. Patients in group A and the control group were significantly taller than those in group B (mean, 161.9 cm vs 157.6 cm; $p = 0.017$; mean, 163.3 cm vs 157.6 cm; $p = 0.003$). Height was not significantly different among groups A and C and the control group. Additionally, patients in group A had a significantly longer duration of diabetes than those in groups B and C (mean, 15.0 years vs 8.7 years and 6.8 years; $p = 0.004$, $p = 0.001$); however, a similar result was not found between groups B and C (8.7 years vs 6.8 years; $p = 0.248$). By Spearman's correlation coefficient, among the factors associated with elasticity indices, only height ($r = 0.27$–0.28) and duration of diabetes ($r = 0.23$–0.27) were slightly significant.

The E_{Mean}, E_{Min}, and E_{Max} SWE elasticity indices for groups A–C and the control group are presented in Table 2. Statistical analysis revealed that the E_{Mean}, E_{Min}, and E_{Max} of the tibial nerve were significantly larger in patients in group A than those in patients in groups B and C and the control group. Patients in group B had larger values of E_{Mean}, E_{Min}, and E_{Max} than patients in group C and the control group. There was no significant difference in terms of nerve stiffness between group C and the control group (Figs. 2 and 3). The E_{Mean}, E_{Min}, and E_{Max} SWE elasticity indices in the tibial nerve from both sides are presented in Table 3. The Wilcoxon rank-sum test revealed no significant difference between the right side and left side in terms of nerve stiffness among groups A–C and the control group.

The ROC curve analyses for the diagnosis of DPN based on the E_{Mean}, E_{Min}, and E_{Max} SWE elasticity indices of the tibial nerve are shown in Fig. 4. In our study, the cutoff values for $E_{Mean,}$ E_{Min}, and E_{Max} for diagnosing DPN that maximized accuracy were 60.2 kPa, 45.7 kPa, and 66.5 kPa, respectively. Table 4 summarizes the sensitivities, specificities, and positive likelihood ratios and negative likelihood ratios on the basis of the E_{Mean}, E_{Min}, and E_{Max} of the tibial nerve when using the optimal threshold values.

The ROC curve analyses revealed that there was no significant difference between the AUC for E_{Min} and E_{Mean} (0.867 vs 0.846, $Z = 0.46$, $p = 0.641$) or between E_{Mean} and E_{Max} (0.846 vs 0.821, $Z = 0.47$, $p = 0.637$) SWE elasticity indices; however, the AUC for E_{Min} was significantly higher than that for E_{Max} (0.867 vs 0.821, $Z = 2.93$, $p = 0.003$). The E_{Min} index had a first-rank AUC for diagnosing DPN with a sensitivity of 0.74 and a specificity of 0.88 based on the AUC analysis (cutoff value, 45.7 kPa).

In terms of the interobserver variability of the stiffness values of E_{Mean}, E_{Min}, and E_{Max}, the ICC were 0.971 (95%

Table 1 Characteristics of the study participants

Clinical characteristic	Group A ($n = 25$)	Group B ($n = 25$)	Group C ($n = 20$)	Control group ($n = 20$)
Age (years)	66.2 ± 12.7	60.9 ± 9.1	57.1 ± 9.6	57.8 ± 15.5
Female sex (%)	14 (56.0)	19 (76.0)	12 (60)	10 (50%)
Height (cm)	161.9 ± 6.7	157.9 ± 5.7	160.8 ± 8.1	163.3 ± 6.6
Weight (kg)	63.7 ± 7.8	60.2 ± 9.5	66.1 ± 12.1	64.8 ± 8.5
Body mass index (kg/m^2)	24.3 ± 2.7	24.2 ± 3.1	25.4 ± 2.8	24.2 ± 2.5
Systolic blood pressure (mmHg)	142.8 ± 23.7	148.9 ± 24.6	141.4 ± 21.9	131.5 ± 23.4
Diastolic blood pressure (mmHg)	78.9 ± 12.7	83.7 ± 14.5	84.2 ± 15.0	75.8 ± 12.6
Diabetes duration (years)	15.0 ± 7.84	8.7 ± 5.8	6.8 ± 6.5	NA
HbA1c (%)	9.0 ± 2.4	7.6 ± 1.4	8.6 ± 1.8	NA

Values are presented as mean ± SD or as a proportion

NA Not applicable

Table 2 Average stiffness values in the tibial nerve for each group

SWE elasticity indices	Group A ($n = 50$ ankles)	Group B ($n = 50$ ankles)	Group C ($n = 40$ ankles)	Control group ($n = 40$ ankles)	p among groups, Kruskal–Wallis
E_{Mean} (kPa ± SD)	64.3 ± 21.6[a,b,c]	48.9 ± 12.2[d,e]	30.9 ± 7.5	32.8 ± 7.1	< 0.01
E_{Min} (kPa ± SD)	54.3 ± 18.4[a,b,c]	39.6 ± 10.4[d,e]	24.6 ± 7.5	26.7 ± 6.6	< 0.01
E_{Max} (kPa ± SD)	74.3 ± 25.9[a,b,c]	57.3 ± 14.6[d,e]	38.2 ± 8.8	39.8 ± 8.6	< 0.01

E_{Mean} mean of SWE elasticity indices, E_{Min} minimum of SWE elasticity indices, E_{Max} maximum of SWE elasticity indices

[a] $p < 0.05$ (group A vs group B) by the Mann–Whitney U test

[b] $p < 0.05$ (group A vs group C) by the Mann–Whitney U test

[c] $p < 0.05$ (group A vs control group) by the Mann–Whitney U test

[d] $p < 0.05$ (group B vs group C) by the Mann–Whitney U test

[e] $p < 0.05$ (group B vs control group) by the Mann–Whitney U test

CI 0.957, 0.981), 0.945 (95% CI 0.918, 0.964), and 0.913 (95% CI 0.871, 0.942), respectively. In terms of the intraobserver variability of the stiffness values of E_{Mean}, E_{Min}, and E_{Max}, the ICC were 0.953 (95% CI 0.929, 0.969), 0.864 (95% CI 0.801, 0.908), and 0.928 (95% CI 0.893, 0.952), respectively.

Discussion

The study showed clearly that tibial nerve stiffness in patients with DPN and clinically defined DPN was significantly greater than in those without DPN and healthy subjects. Tibial nerve stiffness in patients with DPN turned out to be significantly greater than in patients with clinically defined DPN. Furthermore, no significant difference was found between patients without DPN and healthy subjects.

Early diagnosis of DPN is essential for prognosis and treatment because early treatment of DPN decreases both short-term and long-term morbidity [18, 19]. A diagnosis of DPN based on clinical features and electrophysiological tests is accurate and broadly used [20–22]; however, there are a substantial number of patients who have the typical symptoms and signs of DPN but have normal electrophysiological features. This phenomenon is considered "clinico-electrophysiological dissociation" and frequently occurs in the early stages of DPN [23, 24]. The change in nerve stiffness may be explained by the following pathophysiological mechanisms. DPN develops due to metabolic disorders associated with chronic hyperglycemia including an accumulation of sorbitol

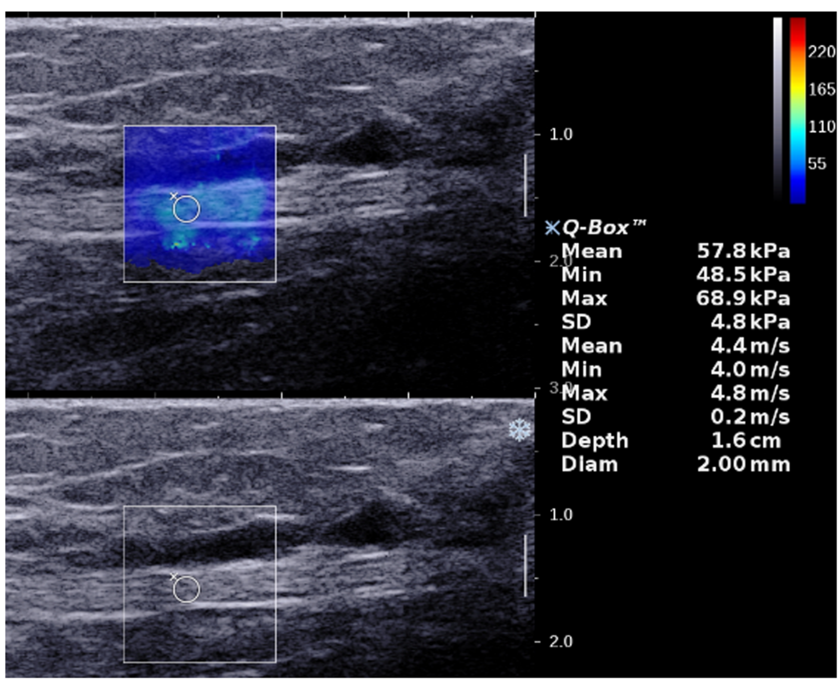

Fig. 2 Shear wave elastography image of the tibial nerve in a 74-year-old female diabetic patient with clinically defined DPN. The E_{Mean}, E_{Min}, and E_{Max} elasticity indices are measured as 57.8, 47.5, and 68.9 kPa, respectively

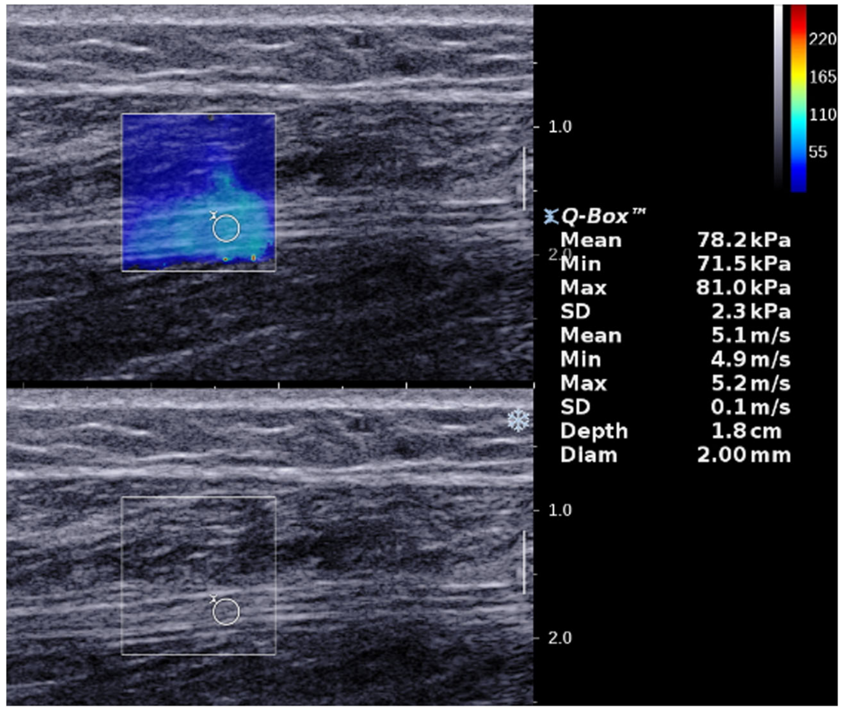

Fig. 3 Shear wave elastography image of the tibial nerve in a 35-year-old female diabetic patient with DPN. The E_{Mean}, E_{Min}, and E_{Max} elasticity indices are measured as 78.2, 71.5, and 81.0 kPa, respectively

and fructose, increased glycation end products, oxidative stress, and lipid alterations that can cause axonal loss combined with demyelination [25, 26]. Sorbitol and secondary sodium accumulation lead to peripheral nerve swelling and increased intraneural pressure. In addition, intraneural pressure may further compress the microvasculature and affect the circulation of the nerve [27]. These pathophysiological changes are presumably recognized as the reason for the increased nerve stiffness that is reflected by SWE measurements. Notably, significantly greater nerve stiffness was detected in patients with clinically defined DPN than in patients without DPN and in control subjects in our study. This finding might suggest that although these patients have normal electrophysiological results, their nerves have probably been affected by diabetes. Some earlier reports [23, 28] have shown that patients in the early stage of diabetes more often have neuropathy restricted to small nerves compared with patients with clinically and electrophysiologically established DPN, who had more involvement of both large and small nerves. However, NCS is more sensitive for detecting changes in large nerve fibers; thus, it might be difficult to detect with NCS small fibers that are damaged early in the course of dysmetabolism.

A previously published study [15] in which 2D-SWE elastography was used to evaluate the tibial nerve in diabetic patients with DPN and without DPN demonstrated increased nerve stiffness in DPN patients. In our study, we enrolled not only patients with DPN and without DPN, but also patients with clinically defined DPN as separated groups and found statistically different nerve stiffness between patients with clinically defined DPN and without DPN. This finding is important because it shows that 2D-SWE has a better correlation with clinical findings than electrophysiology. It can be used to determine if

Table 3 Stiffness values in the tibial nerve from both sides

	E_{Mean} (kPa ± SD)			E_{Min} (kPa ± SD)			E_{Max} (kPa ± SD)		
	Right tibial nerve	Left tibial nerve	*p* value	Right tibial nerve	Left tibial nerve	*p* value	Right tibial nerve	Left tibial nerve	*p* value
Group A	63.2 ± 19.3	65.4 ± 24.0	0.914	53.3 ± 16.6	55.2 ± 20.2	0.715	72.3 ± 22.7	76.2 ± 29.0	0.407
Group B	49.8 ± 12.0	48.0 ± 12.6	0.307	40.0 ± 10.5	39.2 ± 10.6	0.658	58.7 ± 14.9	55.8 ± 14.4	0.207
Group C	30.1 ± 8.3	31.7 ± 6.6	0.313	23.9 ± 8.3	25.3 ± 6.7	0.184	37.1 ± 9.9	39.3 ± 7.5	0.338
Control group	32.3 ± 8.2	33.3 ± 6.0	0.376	27.1 ± 7.7	26.3 ± 5.6	0.794	39.0 ± 9.2	40.6 ± 8.2	0.376

E_{Mean} mean of SWE elasticity indices, E_{Min} minimum of SWE elasticity indices, E_{Max} maximum of SWE elasticity indices

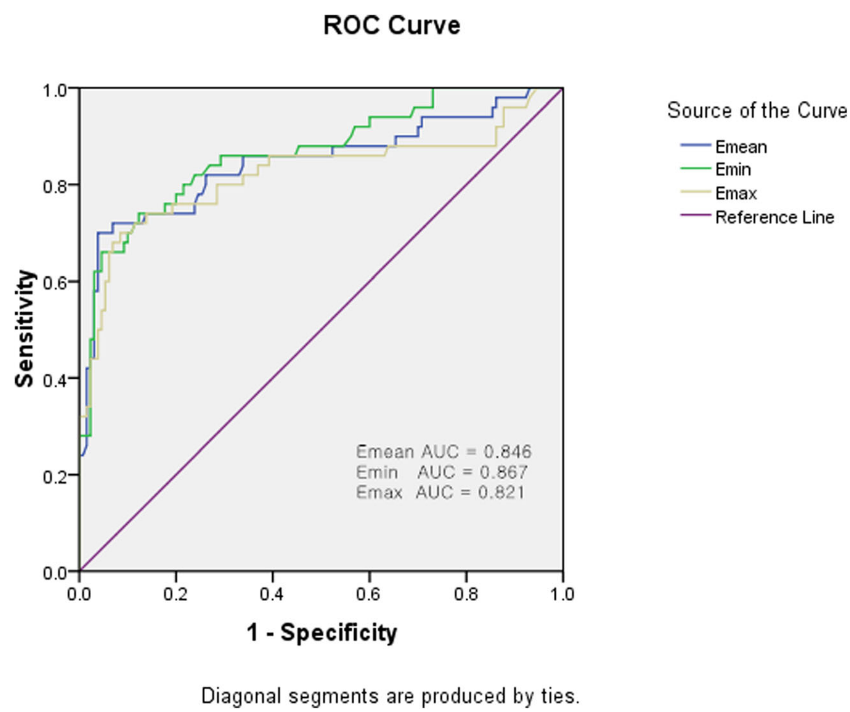

Fig. 4 ROC curve for the diagnosis of DPN based on the E_{Mean}, E_{Min}, and E_{Max} of SWE measurements

minor alterations exist in patients with typical clinical features. In addition to previous reports [8, 13, 16], we measured three different SWE elasticity indices (E_{Mean}, E_{Min}, and E_{Max}) to diagnose DPN. We demonstrated that E_{Min} and E_{Mean} had a better accuracy for identifying DPN. A cutoff of 45.7 kPa on E_{Min} had moderate sensitivity (74.0%) and high specificity (87.6%). In addition, though the sensitivity (70%) of E_{Mean} was lower than that of E_{Min}, E_{Mean} had a better specificity (95%) than E_{Min}. We also analyzed the likelihood ratio which is particularly useful because its assessment enables incremental value of the diagnostic test [29]. E_{Mean} had a strong positive likelihood ratio (18.2). Under these circumstances, if the LR+ of a diagnostic method is more than 10, we may conclude that the gold standard is most probably positive when the diagnostic method yields positive results. Additionally, the inter- and intraobserver variabilities of E_{Mean}, E_{Min}, and E_{Max} were excellent, with ICC values of more than 0.80.

There are several limitations. First, the number of participants in each group was restricted and patients with type I diabetes mellitus were not enrolled in this study; thus, larger sample studies are needed to determine whether these results are robust. Second, SWE measurements were obtained from only tibial nerve and one anatomical level; changes in stiffness of other nerves, such as plantar nerve, were not explored. Third, we did not conduct a stepwise forward multiple regression analysis to correlate the SWE elasticity indices with nerve conduction velocity and other parameters because the velocities from the patients we enrolled were almost normal in this study. Another issue was that increased nerve stiffness is not specific for diabetes mellitus, since other diseases could be confounders [30].

In conclusion, the stiffness of the tibial nerve in diabetic patients with DPN or clinically defined DPN was markedly higher than in patients without DPN and healthy volunteers. E_{Min} and E_{Mean} SWE elasticity indices had better accuracy than E_{Max} for identifying DPN. 2D-SWE elastography is a noninvasive and reproducible method for the precise evaluation of nerve stiffness and is potentially useful when a suspected neuropathy is not detectable by electrophysiology.

Table 4 Sensitivity, specificity, and positive and negative predictive values according to cutoff values

	Cutoff value (kPa)	Sensitivity (%)	Specificity (%)	LR(+) (%)	LR(−) (%)	AUC
E_{Mean}	60.1	70.0 (55.4–82.1)	95.3 (91.3–98.7)	18.2 (7.6–43.8)	0.3 (0.2–0.5)	0.846 (0.785–0.985)
E_{Min}	45.7	74.0 (59.7–85.4)	87.6 (80.8–92.8)	6.0 (3.7–9.8)	0.3 (0.2–0.5)	0.867 (0.808–0.913)
E_{Max}	66.5	70.0 (55.4–82.1)	91.5 (85.4–95.7)	8.3 (4.6–15.0)	0.3 (0.2–0.5)	0.821 (0.758–0.874)

Numbers in parentheses are 95% CIs

LR(+) positive likelihood ratio, *LR(−)* negative likelihood ratio, *AUC* area under the receiver operating characteristic curve

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Ran Haitao.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• Prospective
• Diagnostic or prognostic study
• Performed at one institution

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