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Original Article

Ultrasound evaluation and grading of neuromuscular disease in lower extremities among diabetic patients

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Abstract: Objective: To explore the clinical utility of ultrasound in evaluating and grading neuromuscular diseases in the lower extremities of patients with diabetes mellitus. Methods: A total of 126 inpatients from the Department of Diabetes at Zhangzhou Affiliated Hospital of Fujian Medical University, China, were recruited from June 2020 to December 2022. The cohort included 69 patients with type 2 diabetes mellitus (T2DM) and diabetic peripheral neuropathy (DPN group) and 57 patients with T2DM but without DPN (non-DPN group). Additionally, 80 healthy controls were included. High-frequency ultrasound was used to scan the common peroneal, sural, and tibial nerves, measuring their transverse (D1) and anteroposterior (D2) diameters, and calculating the cross-sectional area (CSA). Changes in the internal echo of the extensor digitorum brevis (EDB) muscle, including maximum thickness and CSA, were also recorded. The DPN group was further subdivided based on disease duration to assess ultrasonic changes over time and the statistical significance of these variations. Results: Ultrasonic changes such as uneven internal echo reduction, ill-defined epineurial boundaries, and obscured cribriform structures were most prevalent in the DPN group. Significant differences in ultrasound parameters (D1, D2, CSA) were observed among the groups (all $P<0.05$), with the most pronounced changes in the DPN group. In patients with a disease duration of over 15 years, a significant increase in CSA of lower extremity nerves and a decrease in CSA of the EDB were noted compared to those in the 5-10 years subgroup (19.89±0.98 vs 19.00±0.94; 5.25±0.74 vs 5.93±0.94; all $P<0.05$). Conclusions: High-frequency ultrasound provides a valuable imaging basis for diagnosing and monitoring DPN, demonstrating significant changes in nerve and muscle parameters among diabetic patients.

Keywords: Ultrasound, diabetes mellitus, neuromuscular disease of the lower extremity, common peroneal nerve

Introduction

Diabetic peripheral neuropathy (DPN) is a common clinical complication in patients with diabetes mellitus (DM), affecting motor, sensory, and autonomic nerves [1]. DPN often leads to sensory and motor dysfunction in the distal extremities, increasing the risk of falls, infections, ulcers, and amputations [2, 3]. Predominantly affecting the lower extremities, DPN is irreversible and can severely impact the quality of life through pain and potentially fatal complications [4].

The pathogenesis of DPN is multifaceted and not fully understood. Peripheral vascular sclerosis is identified as a primary pathological change [5, 6]. Diagnosing DPN typically involves clinical assessments, symptom scoring, and neuro-electrophysiological tests [7]. However, subjective patient responses and the insensitivity of nerve conduction studies to small or unmyelinated fibers can lead to diagnostic errors [8, 9].

High-frequency ultrasound (HFUS) offers detailed visualizations of peripheral nerves, their paths, and relationships with surrounding tissues, providing valuable data for clinical diagnosis and management [10]. HFUS is non-invasive, patient-friendly, and delivers real-time, dynamic, high-resolution images for accurate diagnostics, gaining widespread acceptance [11]. Despite its advantages, HFUS remains underutilized in diagnosing peripheral neuropathy in type 2 diabetes mellitus (T2DM), particularly in the lower extremities [12].

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This study aims to fill this gap by analyzing ultrasonic images and parameters of lower extremity nerves in T2DM patients, with and without DPN. By examining changes in various ultrasonic parameters and performing correlation analyses, this research seeks to establish a reliable imaging framework for DPN diagnosis, thereby aiding in the timely intervention and reduction of DPN progression and prevalence.

Materials and methods

Study subjects

This retrospective analysis was conducted at the Department of Diabetes, Zhangzhou Affiliated Hospital of Fujian Medical University, China, from June 2020 to December 2022. It included 126 inpatients: 69 with diabetic peripheral neuropathy (DPN) of the lower extremities (DPN group) and 57 without DPN (non-DPN group). Additionally, 80 healthy volunteers were recruited for the normal group.

Inclusion criteria: (1) Diagnosis of DM adhering to the 1999 World Health Organization criteria for T2DM [13]; (2) Diagnosis of DPN based on the Clinical Diagnosis and Treatment Criteria for DPN; (3) Completion of lower extremity ultrasound examinations; (4) Availability of complete clinical data.

Exclusion criteria: (1) Type 1 DM; (2) Prior lower extremity surgery; (3) History of lumbar conditions or traumas; (4) Cerebrovascular diseases such as thrombosis or hemorrhage; (5) Peripheral neuropathy (PN) due to neurotoxic drugs or uremia; (6) Incomplete clinical data. Ethical approval for the study was granted by the Ethics Committee of Zhangzhou Affiliated Hospital of Fujian Medical University.

Examination methods

Ultrasounds were performed using a Logiq E9 ultrasound machine (GE, USA) equipped with a 6-15 MHz high-frequency probe. The examinations of nerves, muscles, and tendons of the lower extremity were conducted in the skeletal muscle mode using two-dimensional (2D) and power Doppler settings, and the lower extremity vessels were assessed in vascular mode with 2D, color Doppler power imaging (CDPI), and pulsed-wave (PW) Doppler. Measurements were taken from the non-dominant side of all subjects. To minimize variability, all scans were independently performed three times by the same experienced sonographer, with over five years of experience, and the average of these measurements was recorded as the final result.

Outcome measures

General data: Clinical data collected from patients included age, gender, body mass index, duration of DM, duration of DPN, fasting blood glucose (FBG), random blood glucose (RBG), and glycosylated hemoglobin (HbA1c) levels.

Symptom Assessment: The severity of PN symptoms in the DPN group was evaluated using the Michigan Neuropathy Screening Instrument (MNSI). This instrument assesses foot appearance, ankle reflexes, and vibration sensation, with higher scores indicating more severe PN symptoms.

Common peroneal nerve (CPN): Patients were positioned prone with knees slightly bent. The examination began in the popliteal fossa, where the tibial nerve (TN) was identified adjacent to the popliteal artery. The probe was then moved laterally to simultaneously visualize the TN and CPN, and further traced upwards to observe their convergence into the sciatic nerve. This confirmed the normal trajectory of the nerves at the popliteal fossa. The probe was then relocated to the lateral side of the popliteal fossa to focus on the CPN, examining the nerve running, epineurium contour, nerve bundle echogenicity, and relationship with surrounding tissues. The transverse diameter (D1) of the CPN was measured at the popliteal fossa. After rotating the probe, the longitudinal view of the CPN was obtained to assess the nerve bundle characteristics and measure the anteroposterior diameter (D2). The cross-sectional area (CSA) of the CPN was calculated using the formula $CSA=D1*D2*\pi/4$.

Sural nerve (SN): The patient was positioned prone. The ultrasound probe was placed behind the mid-calf to locate the small saphenous vein adjacent to the SN. Observations were made of the SN's internal structure and its relationship with surrounding tissues. Measurements of the D1 and D2 were taken at the inner edge of the epineurium, and the CSA was calculated.

Superficial peroneal nerve (SPN): The patient assumed a seated position with knees bent. The probe was placed on the anterolateral aspect of the middle to lower one-third of the calf to locate the SPN between the peroneus brevis and the extensor digitorum longus, beneath the epimuscular fascia. The internal structure and surrounding tissues of the SPN were assessed. The outer edges were traced to measure D1 and D2, and the CSA was calculated.

TN: The patient was supine with the tibia externally rotated. The probe was positioned transversely at the medial malleolus to precisely locate the short axis of the posterior tibial artery and vein. The TN was scanned from the popliteal fossa to the sole of the foot. The probe was then rotated to provide a longitudinal view, observing the TN's course, epineurium contour, nerve bundle echogenicity, and its proximity to surrounding tissues. D1 and D2 were measured 4 cm above the highest point of the medial malleolus, and the CSA was calculated.

Extensor digitorum brevis (EDB): The patient was placed in a supine position with the foot dorsiflexed to enhance visibility of the EDB. Measurements were conducted using the lateral malleolus and the tuberosity of the fifth metatarsal as anatomical landmarks. A vertical line drawn at the midpoint between these two points served as the placement guide for the ultrasound probe. The maximum thickness and CSA of the EDB were measured along this line. Care was taken to use a sufficient amount of ultrasonic coupling gel and to place the probe lightly on the skin to prevent compression of the subcutaneous muscle, which could affect measurement accuracy. The probe was adjusted to be perpendicular to the muscle surface, and the maximum CSA was determined using the inner edge of the muscle fascia surrounding the EDB as the boundary.

Statistical analysis

Data were analyzed using SPSS version 25.0. The significance threshold was set at $P<0.05$. Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm sd$) and analyzed using analysis of variance for multi-group comparisons, the LSD-t test for pairwise comparisons, the t-test for between-group and paired t-tests for within-group comparisons. Categorical variables were presented as proportions and analyzed using the Chi-square (χ^2) test. Correlations between variables were assessed using Spearman's rank correlation coefficient.

Results

General data

Statistical analysis of clinical data from two diabetic patient groups and concurrent healthy volunteers revealed no significant differences in age, gender, or body mass index among the three groups (all $P>0.05$). Similarly, no significant differences were observed in the duration of DM between the DPN and non-DPN groups ($P>0.05$). However, both diabetic groups exhibited significantly higher levels of FBG, RBG, and HbA1c than the normal group (all $P<0.05$). Notably, significant differences were also present between the DPN and non-DPN groups in terms of FBG and HbA1c levels (both $P<0.05$), as summarized in **Table 1**.

Comparison of CPN ultrasound abnormalities

In the DPN group, significant ultrasound abnormalities were noted in the CPN: reduced nerve bundle echo (75.4%), blurred cribriform structure (75.4%), uneven thickening of the epineurium (31.9%), and ill-defined boundaries with adjacent tissues (65.2%). These abnormalities were significantly higher compared to those observed in the non-DPN and normal groups (all $P<0.05$, **Table 2**).

Comparison of TN ultrasound abnormalities

In the normal group, the TN appeared oval-shaped and hyperechoic on transverse sections with a clear internal cribriform structure, while longitudinal sections displayed a cord-like linear hyperecho with a distinct course and well-defined epineurial boundaries. Conversely, in the DPN group, significant proportions of TN abnormalities were recorded: reduced nerve bundle echo (69.6%), blurred cribriform structure (71.0%), uneven thickening of the epineurium (76.8%), and ill-defined boundaries with surrounding tissues (79.7%). These findings were significantly more prevalent than those in the other two groups (all $P<0.05$, **Table 3** and **Figure 1**).

Table 1. General data of patients

	DPN (n=69)	Non-DPN (n=57)	Normal (n=80)	F/χ^2/t	P
Age (years)	55.14±9.46	54.85±9.78	54.74±10.23	0.138	0.871
Gender (n)				1.049	0.592
Male	39	27	42		
Female	30	30	38		
BMI (kg/m^2)	21.91±3.14	22.49±2.84	22.09±3.05	0.743	0.477
Course of diabetes mellitus (years)	13.81±4.20	14.16±4.86		0.434	0.665
Course of DPN (years)	4.77±0.63				
Fasting blood glucose (mmol/L)	8.76±1.31	9.93±1.43*	5.07±0.96$^{*,\#}$	305.1	<0.0001
Random blood glucose (mmol/L)	11.86±3.40	11.95±3.29	7.19±1.69$^{*,\#}$	68.14	<0.0001
Glycosylated hemoglobin (%)	9.62±1.78	8.68±1.33*	5.45±1.09$^{*,\#}$	177.4	<0.0001

Note: DPN: diabetic peripheral neuropathy; BMI: body mass index. Compared with the DPN group, *P<0.05; compared with the non-DPN group, $^{\#}$P<0.05.

Table 2. Comparison of common peroneal nerve ultrasound abnormalities among the three groups

	Reduced nerve bundle echo (n)	Blurred cribriform structure (n)	Blurred epineurium (n)	Ill-defined boundaries with adjacent tissues (n)
DPN (n=69)	52 (75.4)	52 (75.4)	22 (31.9)	45 (65.2)
Non-DPN (n=57)	23 (40.4)*	20 (35.1)*	7 (12.3)*	5 (8.8)*
Normal (n=80)	2 (2.5)$^{*,\#}$	3 (3.8)$^{*,\#}$	2 (2.5)$^{*,\#}$	2 (2.5)$^{*,\#}$
χ^2	84.402	82.122	24.652	88.552
P	<0.0001	<0.0001	<0.0001	<0.0001

Note: DPN: diabetic peripheral neuropathy. Compared with the DPN group, *P<0.05; compared with the non-DPN group, $^{\#}$P<0.05.

Table 3. Comparison of tibial nerve ultrasound abnormalities among the three groups

	Reduced nerve bundle echo (n)	Blurred cribriform structure (n)	Blurred epineurium (n)	Ill-defined boundaries with adjacent tissues (n)
DPN (n=69)	48 (69.6)	49 (71.0)	53 (76.8)	55 (79.7)
Non-DPN (n=57)	29 (50.9)*	27 (47.4)*	24 (42.1)*	8 (14.0)*
Normal (n=80)	4 (5.0)$^{*,\#}$	3 (3.8)$^{*,\#}$	2 (2.5)$^{*,\#}$	2 (2.5)$^{*,\#}$
χ^2	62.372	63.062	87.002	113.520
P	<0.0001	<0.0001	<0.0001	<0.0001

Note: DPN: diabetic peripheral neuropathy. Compared with the DPN group, *P<0.05; compared with the non-DPN group, $^{\#}$P<0.05.

Comparison of ultrasonic measurement parameters of nerves

Analyses of multiple ultrasonic parameters showed significant differences among the three groups in terms of the D1, D2, and CSAs of the CPN, TN, SN, and SPN (all P<0.05), with the highest values found in the DPN group (P<0.05, **Table 4**).

Correlation analysis

In the DPN group, the MNSI score averaged (4.73±1.09) points, demonstrating a positive correlation with the CSA of the CPN, TN, SN, and SPN (r=0.414, r=0.376, r=0.383, r=0.280; all P<0.05, **Figure 2**).

Ultrasonic measurements of dorsalis pedis muscle

The DPN group showed a significant reduction in the maximum thickness and CSA of the EDB compared with the non-DPN and normal groups. The maximum thickness and CSA of the EDB in the non-DPN group were also significantly lower than those in the normal group (both P<0.05, **Table 5**).

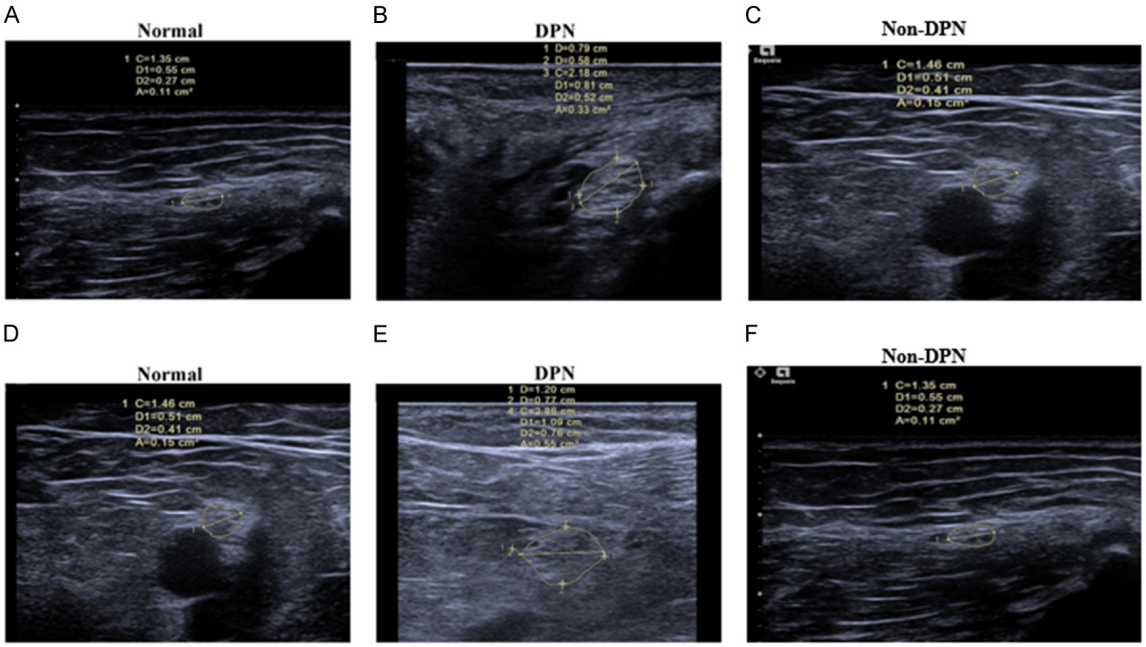

Figure 1. Ultrasound images of the nerves in the normal, DPN, and non-DPN groups. Note: A: Ultrasound image of the transverse section of the tibial nerve in the normal group: Clear cribriform structure of the nerve bundle, with well-defined boundaries with the surrounding tissues; C: Ultrasound image of the transverse section of the common peroneal nerve in the normal group: Clear cribriform structure of the nerve bundle, with well-defined boundaries with the surrounding tissues; B, E: Ultrasound image of the nerve: Swollen nerve bundle, with enhanced echo, blurred cribriform structure and epineurium, and ill-defined boundaries with the surrounding tissues; D, F: Ultrasound image of the common peroneal nerve: Swollen nerve bundle, with enhanced echo, blurred cribriform structure and epineurium, and ill-defined boundaries with the surrounding tissues. DPN: diabetic peripheral neuropathy.

Ultrasonic measurement parameters of the lower extremities in patients with different courses of disease

In the DPN group, there were 24, 29, and 16 patients with a course of DM more than 15 years, 10-15 years, and 5-10 years, respectively. The CSAs of the CPN, TN, SN, and SPN increased significantly in patients with a course of more than 15 years compared to those with a course of 5-10 years, while the thickness and CSA of the EDB decreased ($P<0.05$). Statistical significance was present in all ultrasonic measurement parameters among the subgroups ($P<0.05$, **Table 6**).

Discussion

Hyperglycemia is a primary factor in the onset of lower extremity PN in T2DM, although the exact mechanisms are not fully understood. The pathogenesis may involve metabolic disturbances, cytokine dysregulation, oxidative stress, neurotrophic factor deficiencies, and vascular damage [14-16]. PN predominantly affects the lower extremities more severely than the upper extremities, characterized by symmetrical lesions that progress and are irreversible. Clarifying the diagnosis of PN is crucial for the effective clinical management of DPN.

In our study, the DPN group exhibited significantly higher instances of reduced nerve bundle echo, blurred cribriform structures, uneven epineurium thickening, and ill-defined boundaries with adjacent tissues in the CPN and TN compared to the non-DPN and normal groups. The proposed mechanisms include diabetes-induced alterations in nerve fibers and sheaths, and vascular structures that may lead to axonal dystrophy, degeneration, and significant nerve fiber loss. Concurrently, local capillary damage may cause interstitial cell proliferation and nerve sheath thickening, resulting in increased nerve diameter [17, 18].

Normal muscle ultrasound typically shows hypoechoic muscle bundles, with hyperechoic myofascial tissues surrounding them. Interfascicular and fibrofat separations appear as

Table 4. Comparison of ultrasonic measurement parameters of nerves

Groups	D1 (mm)	D2 (mm)	CSA (mm^2)
Common peroneal nerve			
DPN (n=69)	6.28±0.27*,#	3.94±0.15*,#	19.45±1.07*,#
Non-DPN (n=57)	5.69±0.32*	3.88±0.14*	17.35±1.07*
Normal (n=80)	5.13±0.19	3.38±0.12	13.61±0.70
F	367.4	383.0	734.6
P	<0.0001	<0.0001	<0.0001
Tibial nerve			
DPN (n=69)	6.73±0.24*,#	4.13±0.08*,#	21.86±0.94*,#
Non-DPN (n=57)	5.93±0.17*	3.87±0.13*	18.03±0.78*
Normal (n=80)	5.20±0.15	3.57±0.11	14.61±0.59
F	1204	507.4	1625
P	<0.0001	<0.0001	<0.0001
Sural nerve			
DPN (n=69)	4.25±0.67*,#	3.13±0.22*,#	10.42±1.73*,#
Non-DPN (n=57)	3.97±0.52*	2.35±0.29*	7.36±1.41*
Normal (n=80)	3.34±0.50	2.07±0.22	5.41±0.86
F	50.38	373.1	254.4
P	<0.0001	<0.0001	<0.0001
Superficial peroneal nerve			
DPN (n=69)	2.04±0.17*,#	2.75±0.19*,#	4.42±0.46*,#
Non-DPN (n=57)	1.68±0.16*	2.29±0.20*	3.02±1.40*
Normal (n=80)	1.40±0.17	2.12±0.22	2.33±0.36
F	271.3	182.5	124.6
P	<0.0001	<0.0001	<0.0001

Note: CSA: cross-sectional area; DPN: diabetic peripheral neuropathy; D1: transverse diameter; D2: anteroposterior diameter. Compared with the normal group, *P<0.05; compared with the non-DPN group, #P<0.05.

linear hyperechoic lines, distinctly demarcated from other tissues. Axial scans often reveal a finely distributed, slightly hyperechoic circular or cribriform structure internally, surrounded by a hyperechoic outer epineurium. In the coronal plane, a thin, parallel hyperechoic tubular structure is visible, containing hypoechoic regions segmented by multiple thin linear hyperechoic strips along the edges of the tubular structure. In cases of muscle atrophy, ultrasound may show irregular internal muscle fiber arrangement with dense fiber gaps and slightly increased overall muscle tissue echogenicity. These findings are consistent with those reported in previous studies [19-21].

Our study findings revealed significantly larger transverse and anteroposterior diameters, as well as CSA of the CPN, TN, SN, and SPN in the DPN group compared to the non-DPN and normal groups. The CPN and SPN, being mixed nerves, are responsible for muscle movement and some sensory functions. Neuropathy in these nerves can lead to muscle weakness, atrophy, and even paralysis, along with sensory abnormalities such as paresthesia, numbness, pain, and hypoesthesia in the affected areas.

HFUS was employed to measure the CSA of the posterior tibial nerve in 98 patients with lower extremity DPN. Measurements were taken approximately 1 cm, 3 cm, and 5 cm from the superior margin of the medial malleolus, and corresponding receiver operating characteristic (ROC) curves were generated. The optimal diagnostic threshold for DPN was found to be a CSA value of 19.01 mm^2 at 3 cm, with a sensitivity of 69% and a specificity of 77%. Additionally, Kang et al. determined that a CSA value of 11.55 mm^2 at the fibulae capitulum for the CPN yielded a sensitivity of 75% and a specificity of 70% for diagnosing DPN [22]. For the SN, when crossing the small saphenous vein, a CSA of 4.15 mm^2 achieved a sensitivity of 80% and a specificity of 70% [23, 24].

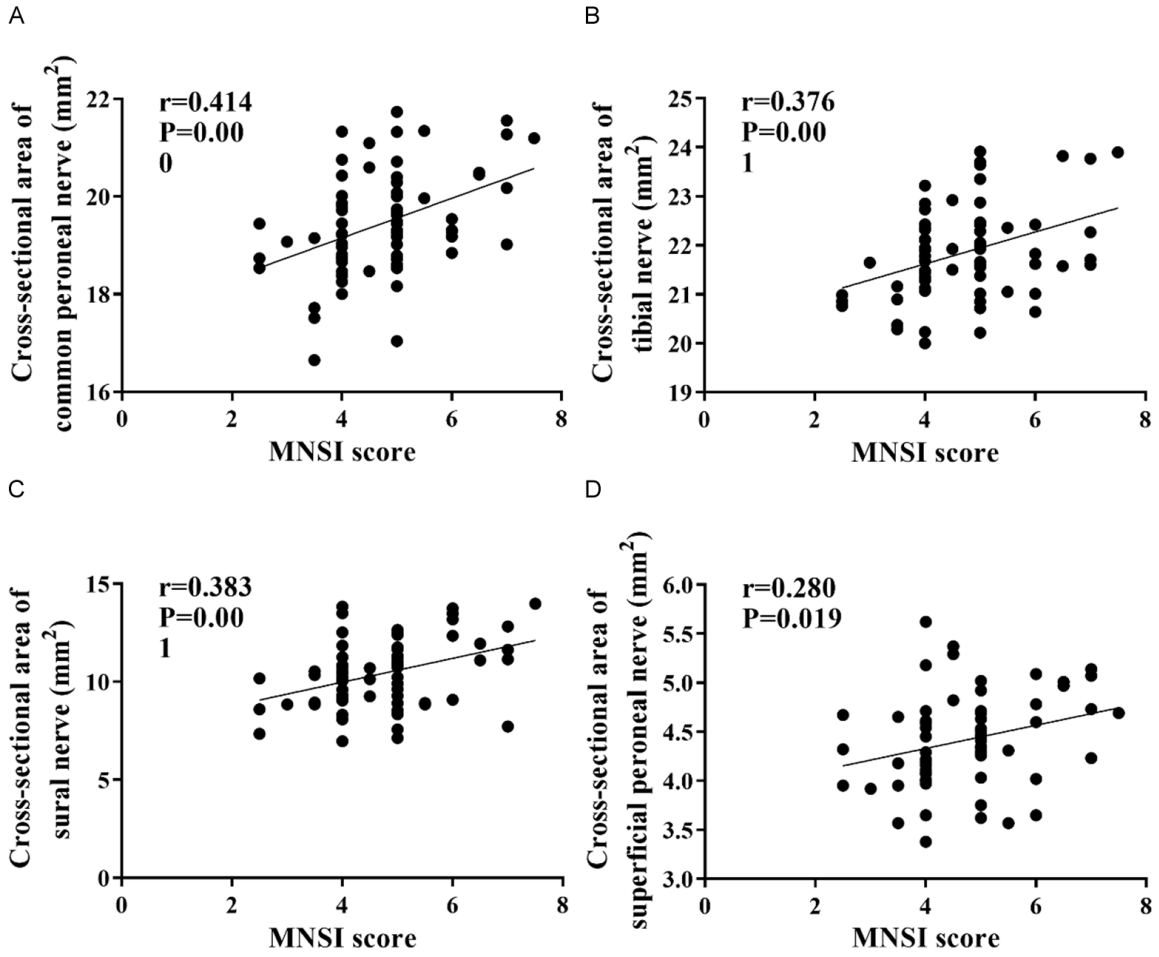

Figure 2. Correlation analysis between MNSI score and nerve cross-sectional area. A: Correlation analysis between MNSI score and cross-sectional area of the common peroneal nerve; B: Correlation analysis between MNSI score and cross-sectional area of the tibial nerve; C: Correlation analysis between MNSI score and cross-sectional area of the sural nerve; D: Correlation analysis between MNSI score and cross-sectional area of the superficial peroneal nerve. Note: MNSI: Michigan Neuropathy Screening Instrument.

Table 5. Comparison of parameters of the extensor digitorum brevis among the three groups

Group	Maximum thickness of the extensor digitorum brevis (mm)	Maximum cross-sectional area (mm^2)
DPN (n=69)	5.54±0.81*,#	90.29±11.36*,#
Non-DPN (n=57)	6.76±0.35*	139.55±14.29*
Normal (n=80)	7.17±0.17	161.82±15.67
F	195.1	498.2
P	<0.0001	<0.0001

Note: DPN: diabetic peripheral neuropathy. Compared with the normal group, *P<0.05; compared with the non-DPN group, #P<0.05.

In this study, we also observed a significant reduction in the maximum thickness and CSA of the EDB in the DPN group compared to the non-DPN and normal groups, indicative of more pronounced muscular atrophy in the dorsum pedis among DPN patients. These findings align with prior research, such as that by Zochodne et al., which highlighted the utility of HFUS in diagnosing EDB muscular atrophy in patients with DPN [24, 25].

The study also compared ultrasonic parameters in patients with varying durations of DM. It was observed that the CSA of each nerve increased with the duration of DM. This suggests that prolonged hyperglycemia exacerbates the met-

Table 6. Comparison of ultrasonic measurement parameters of the lower extremities in patients with different courses of disease

Courses of disease	5< Years ≤10	10< Years ≤15	>15 Years	F	P
Number of patients (n)	16	29	24		
CSA of the common peroneal nerve (mm^2)	19.00±0.94	19.33±1.10	19.89±0.98*,#	4.193	0.019
CSA of the tibial nerve (mm^2)	21.26±0.82	21.93±0.83	22.17±1.01*	5.127	0.008
CSA of the sural nerve (mm^2)	9.67±1.53	10.31±1.74	11.06±1.66*	3.454	0.037
CSA of the superficial peroneal nerve (mm^2)	4.20±0.44	4.40±0.44	4.58±0.45*	3.557	0.034
Thickness of the extensor digitorum brevis (mm)	5.93±0.94	5.55±0.72	5.25±0.74*	3.640	0.032
CSA of the extensor digitorum brevis (mm^2)	95.83±13.15	90.08±11.37	85.76±9.90*	3.799	0.027

Note: CSA: cross-sectional area. Compared with the 5< Years ≤10 group, *P<0.05; compared with the 10< Years ≤15 group, #P<0.05.

abolic disorder, leading to more severe damage to the lower extremity nerves and dorsalis pedis muscles through neuropathy, microangiopathy, oxidative stress, and advanced glycation end products, resulting in pronounced morphological changes. These findings are consistent with previous research [26]. Effective blood glucose management can mitigate CSA changes, alleviate symptoms, and decelerate the progression of DPN.

This study evaluated the efficacy of HFUS in diagnosing lower extremity PN in T2DM patients. HFUS proved valuable in providing diagnostic imaging support for T2DM with lower extremity PN. However, the study was limited by its single-center, small sample size, and retrospective nested case-control design, which may introduce bias. Future studies should aim for a multi-center approach with a larger sample size to validate these findings further.

In conclusion, HFUS offers critical imaging evidence for diagnosing T2DM with lower extremity PN. Its utilization of multiple parameters can effectively assess lesions during DPN progression, aiding in improved clinical treatment and enhancing the long-term quality of life for patients with DPN.

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Disclosure of conflict of interest

None.

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