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The feasibility of using high-resolution ultrasonography to assess ulnar nerve in patients with diabetes mellitus

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Keywords
high-resolution ultrasonography, ulnar nerve, diabetes mellitus, peripheral

Abstract

Objective: The aim of this study was to investigate the usefulness of high-resolution ultrasonography for the diagnosis of polyneuropathy in diabetes mellitus patients by the examination of the ulnar nerves. **Method:** We recruited 100 healthy age-matched volunteers (50 women and 50 men) with 200 arms without diabetes or cubital tunnel syndrome as the control group. We assessed the upper limbs of 100 diabetes mellitus patients (45 women and 55 men), 40 of whom had electrophysiologically confirmed diabetic peripheral neuropathy and 60 had no diabetic peripheral neuropathy in the upper limbs. Age, sex, height and weight were recorded and the cross-sectional area of the ulnar nerve was measured at every predetermined site. **Results:** The cross-sectional area of the ulnar nerve was measured at six sites (mid-humerus, inlet of the cubital tunnel, outlet of the cubital tunnel, upon the medial epicondyle, 6 cm upon the wrist crease and Guyon tunnel). The ulnar nerve in two measuring sites (mid-humerus, upon the medial epicondyle) in the control group showed a statistical difference between men and women ($p < 0.05$). There was no statistical difference in the cross-sectional area in the control group when dominant and non-dominant arms were compared. The cross-sectional area was larger in the diabetic peripheral neuropathy group in three sites (inlet of the cubital tunnel, outlet of the cubital tunnel, Guyon tunnel) compared with those in the control group. **Conclusion:** High-resolution ultrasonography may be helpful in the early diagnosis of peripheral neuropathy in diabetic patients.

Introduction

Diabetic polyneuropathy is an insidious and long-term complication of diabetes. Diabetes mellitus is a group of physiological dysfunctions characterized by hyperglycemia resulting directly from insulin resistance, inadequate insulin secretion or excessive glucagon secretion. Glucose neurotoxicity has been suggested by plenty of evidence[1]. Diabetic polyneuropathy (DPN) is the most common long-term complication of diabetes mellitus and affects more than 50% of patients[2]. Distal symmetric polyneuropathy is the most common type of peripheral neuropathy; the clinical features may be distinct due to different nerve fibers damaged. Painful diabetic peripheral neuropathy impairs the quality of life and can be difficult to treat[3]. Traditionally, peripheral nerve lesions are diagnosed on the basis of clinical history, physical examination and electrophysiological studies, and the role of imaging studies has been limited[4]. Nowadays, however, in order to detect early neuropathy, one needs to use electrophysiology.

The aim of this study was to determine the criteria for ultrasonographic measurement of the cross-sectional

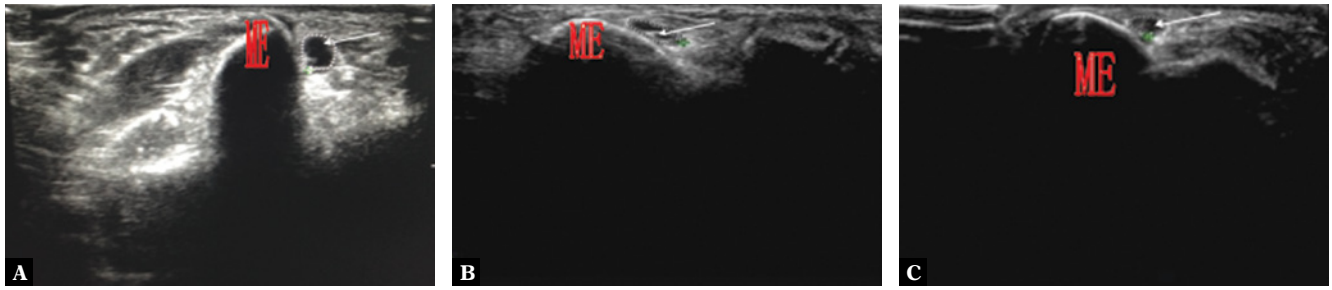


Fig. 1. A. *Inlet of the cubital tunnel in the diabetic peripheral neuropathy group. The ulnar nerve is depicted by bright arrows. The cross--section of the ulnar nerve is 0.179 mm², the nerve is the circular hypoechoic structure. ME: medial epicondyle.* **B.** *Inlet of the cubital tunnel in the diabetes mellitus group; the nerve is the oval hypoechoic structure. ME: medial epicondyle. The cross-section of the ulnar nerve is 0.90 mm².* **C.** *Inlet of the cubital tunnel in the control group. The cross-section of the ulnar nerve is 0.87mm²: the nerve is the oval hypoechoic structure*

area (CSA) of the ulnar nerve and perform differential diagnosis of patients with or without diabetic polyneuropathy (DPN). However, the standard criteria for diagnosing diabetic peripheral neuropathy with high-resolution ultrasonography are not well established, especially in diabetic patients suspected of diabetic peripheral neuropathy. In order to evaluate treatment options for neuropathic pain and sensory symptoms resulting from diabetic peripheral neuropathy, accurate diagnosis of peripheral neuropathies can be made with the use of clinical and electrophysiological tests. In recent years, due to improved technology, high-resolution ultrasonography has been regarded as an inexpensive, reproducible and more comfortable technique, and it can be utilized as an alternative method for detecting neuropathies. Most studies have investigated peripheral nerves at the vulnerable sites, such as the median nerve at the carpal tunnel and the tibial nerve at the medial malleolus in diabetic patients[2]. Most of the measurements done in diabetics are with the goal of defining diabetic neuropathy by evaluating the loss of neuron function. The cross-sectional area of the ulnar nerve was measured with high-resolution ultrasonography (HUS). Ulnar nerve entrapment is the second most common compressive neuropathy in the upper extremity because of the anatomy and superficial location of the nerve[5]. The nerve ending problem is one of the major causes of diabetic feet[6]. The aim was to raise the clinical diagnostic rate of type 2 diabetes patients with peripheral polyneuropathy who were diagnosed for the first time through the combination of electromyography and high-resolution ultrasonography. In the absence of normative reference values of the ulnar nerve, the contralateral limb may be used as the comparative control[7] for ultrasonographic measurements of the ulnar nerve in the upper extremity.

High-resolution ultrasound is the most commonly used imaging modality because it is inexpensive, provides high resolution, is readily available and allows for dynamic imaging. Most studies suggest that the key ultrasonographic finding is enlargement of the ulnar nerve at the site of neuropathy. We designed this current study using the same ultrasonographic technique to determine which measurement best differentiates those with ulnar neuropathy from normative, healthy controls.

Method

Methods: One hundred volunteers with normal neural electrophysiological examination results were recruited by advertisement. The recruited individuals included medical and hospital staff who had no numbness, pain or weakness. Individuals were excluded if they experienced numbness, tingling, pin and needles sensation, pain or weakness in their hand or arm[8]. The study protocol was approved by the institutional review board, and all subjects gave written informed consent. Diabetes mellitus (DM) was diagnosed according to the criteria of the World Health Organization as follows: 1) fasting plasma glucose > 126 mg/dl (7.0 + mmol/l), where fasting was defined as no caloric intake for at least 8 hours 2) symptoms of hyperglycemia and random plasma glucose > 200 mg/dl (11.1 mmol/l), where random was defined as any time of day without regard to time since last meal; or 3) 2-h plasma glucose > 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test. All patients diagnosed with diabetes mellitus neuropathy in the upper extremity had clinical symptoms (pain, numbness). We excluded patients with previous ulnar nerve surgery, polyneuropathy, and acute traumatic etiology. We assessed the upper limbs of 100 diabetes mellitus patients (45 women and 55 men), 40 of whom had electrophysiologically confirmed diabetic peripheral neuropathy and 60 had no diabetic peripheral neuropathy in the upper limbs.

Diabetes mellitus patients were divided into two groups. They were assessed and underwent high-resolution ultrasonography of the ulnar nerve. There were no obvious significant differences in age, height, and weight when we compared the diabetes mellitus group with the control group. High-resolution ultrasonographic measurements of ulnar nerve dimensions in the upper extremity were compared between 2 groups of subjects: symptomatic and asymptomatic. The HUS examiner was blinded to these test results. The CSA of the ulnar nerve was measured at six sites [mid-humerus (MH), inlet of the cubital tunnel (ICT), outlet of the cubital tunnel (OCT), upon the medial epicondyle (UME), 6 cm upon the wrist crease (UWR), Guyon tunnel (GT)] (Fig. 1), and the difference in the CSA between the diabetes mellitus group

Characteristics	Control group	Diabetes mellitus group	Diabetic peripheral neuropathy group
N	100	60	40
Age (year)^	58.5 ± 7.7	61.5 ± 7.0#	59.6 ± 6.9#*
Sex (male/female)	59/41	33/27	18/22
Height (cm)^	168.7 ± 8.9	164.4 ± 7.6#	160.7 ± 6.8#*
Weight (kg)^	51.3 ± 6.8	55.8 ± 7.1#	53.6 ± 6.2#*
Handedness (left/right)	100/100	60/60	40/40

^ Data are expressed as the mean ± SD.
There were no obvious significant differences in age, height, weight when we compared the diabetes mellitus group and the diabetic peripheral neuropathy group with the control group.
Compared with the control group $p > 0.05$.
* Compared with the diabetes mellitus group $p > 0.05$.

Tab. 1. *Basic data of subjects*

and the diabetic peripheral neuropathy group was calculated. The CSA of the ulnar nerve was measured by tracing along the hyperechoic rim of the nerve. Each measurement was taken three times and the average was recorded[9].

High-resolution ultrasonography was performed with a linear array transducer of 15 MHz (Philip iu22 made in the USA). An ultrasound examination doctor blinded to all participant information performed the ultrasound studies. Systemic and nerve examinations (light touch, pinprick, position, temperature, vibration senses) were performed by a clinician who was blinded to the results of the nerve conduction studies (NCSs). The transducer was placed perpendicular to the nerves on the skin, and no additional pressure was applied other than its own weight. The CSA was measured by tracing the nerve just inside its hyperechoic rim, and three measurements were obtained with the probe repositioned. The average value was used for each level.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and compared among the groups. Continuous variables comparison between the two groups was performed using the Student t test. Multiple mean comparison was analyzed by one-way analysis of variance (ANOVA) followed by a post hoc LSD test.

Statistical analysis was performed using the SPSS statistical software for Windows version 11.5 (SPSS, Inc., Chicago, Ill., USA). $P < 0.05$ was considered statistically significant. The demographic data of the study participants are shown in Table 1. This study involved Chinese patients with T2DM with (n = 40) or without (n = 60) diabetic peripheral neuropathy (DPN) and the control subjects (n = 100). The ulnar nerve CSA was significantly larger in the DM-DPN group than in the non-DPN group and controls in some measuring sites ($p < 0.05$). There was no significant difference in terms of age, sex, and body height among the three groups.

Results

The clinical characteristics of the subjects are presented in Table 1. The CSA of the ulnar nerve in those with diabetes mellitus in some measuring sites was greater than that in the control group (Fig. 1). No difference was detected in the CSA of ulnar nerve between the diabetes mellitus group and the diabetic peripheral neuropathy group. The CSA in healthy volunteers in three sites (ICT, OCT, GT) was smaller than that in the diabetes mellitus peripheral neuropathy group. The ulnar nerve in two measuring sites (MH, UME) in the control group showed a statistical difference between men and women ($p < 0.05$); there was no statistically significant difference in other measuring sites between men and women (Tab. 2). There was no statistical difference in the CSA in the control group when dominant and non-dominant upper extremities were compared (Tab. 3). The CSAs were larger in the diabetic peripheral neuropathy group in three sites (ICT, OCT, GT) compared with those in the control group (Tab. 4). The CSA of the ulnar nerve in other sites (MH, UME, UWR) revealed no significant differences between the diabetic peripheral neuropathy group and the control group (Tab. 4). Data from three measurements were compared among the groups. Figure 2 shows a clear difference between the means of the three sets of data in a histogram form. There was a statistically significant difference in two measuring sites (OC, GT) between the control group and the diabetes mellitus group. The CSA level of the diabetes mellitus group in six sites was significantly lower than that of the diabetic peripheral neuropathy group, but there were no statistically significant differences. In terms of internal echogenicity the nerves in diabetic peripheral neuropathy were hypoechoic or anechoic in a few measuring sites. High frequency ultrasound may be helpful in the early diagnosis of peripheral neuropathy in diabetic patients.

Discussion

Diabetic polyneuropathy occurs in around 50% of diabetic patients. Its pathophysiological mechanism is not completely clear and major occurrences boil down to

Control group	Number	Mid-humerus	Inlet of the cubital tunnel	Outlet of the cubital tunnel	Upon the medial epicondyle	6 cm upon the wrist crease	Guyon tunnel
Right side	100	5.58 ± 1.33	6.40 ± 1.39	6.31 ± 1.31	5.89 ± 1.47	5.02 ± 1.27	4.82 ± 1.17
Left side	100	5.62 ± 1.36	6.37 ± 1.37	6.21 ± 1.29	5.85 ± 1.38	4.98 ± 1.16	4.91 ± 1.28
***P*-value**		0.69	0.64	0.78	0.84	0.75	0.92
P-values < 0.05 were considered statistically significant.							

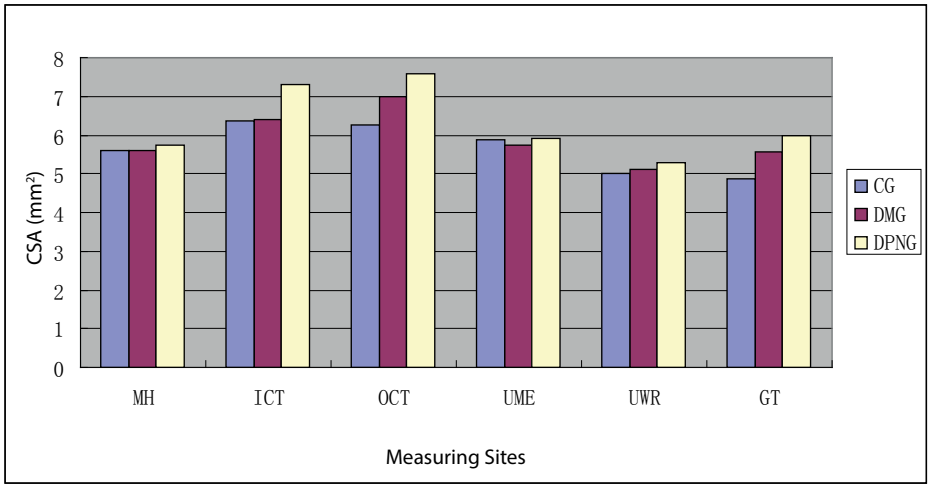
Tab. 2. *CSA of ulnar nerve on both sides in the control group (mean ± SD) (mm²)*

the change in neural phenotype and vasa nervorum[1]. Diabetic polyneuropathy (DPN) is the most common long-term complication of diabetes mellitus. Glucose neurotoxicity has been suggested by plenty of evidence[1]. Diabetic polyneuropathy can affect any part of the nervous system (distal, proximal, large, small, motor, or autonomic fibers). The aim of this study was to determine the criteria for ultrasonographic measurement of the cross-sectional area (CSA) of the ulnar nerve for differential diagnosis of patients with or without diabetic polyneuropathy. However, the standard criteria of diabetic peripheral neuropathy by high-resolution ultrasonography are not well established, especially in diabetic patients suspected of diabetic peripheral neuropathy. In recent years, due to improved technology, ultrasonography has been regarded as an inexpensive, reproducible, and more comfortable technique, and it can be utilized as an alternative method for detecting neuropathies. The ulnar nerve at the upper extremity was easily imaged using ultrasound.

Compressive neuropathy of the ulnar nerve in the upper extremity is a common problem that frequently results in severe disabilities. Normally, the ulnar nerve is subjected to stretch and compression forces that are moderated by its ability to glide in its anatomic path around the elbow. When normal excursion is restricted, irritation ensues[10]. In ultrasonographic images, healthy ulnar nerves appear as cable-like structures that consist of hypoechoic fascicles and hyperechoic surrounding epineurium. In routine practice, a 15 MHz linear array transducer can be employed to scan the entire ulnar nerve in both the transverse and longitudinal planes, and display variation in the shape of the nerve from a flat oval at upon the medial epicondyle to a circle at the Guyon tunnel. Given the observed variation in the shape of the nerve from a flat oval at the wrist to a circle at the upper extremity level, it may be speculated that the CSA is a more consistent index for measurement. The CSA is a more reliable measurement than the diameter[11,12]. The ulnar nerve in two measuring sites (MH, UME) in the control group showed a statistical difference between men and women ($p < 0.05$). The precise reason for such discrepancy is largely unknown at this time. Much of this variability may be due to differences in measurement techniques, along with differences between the populations studied. This sex-specific information could help define normal and abnormal states. The information on side-to-side variation and sex-specific differences will be particularly helpful for the diagnosis of peripheral neuropathies. Our study suggests that the biggest CSA of ulnar nerve in the upper extremity is at the MH measuring site. The difference between the diabetes mellitus group and the diabetic peripheral neuropathy group in six sites has no statistical significance. There was no statistical difference in nerve size in the control group between the dominant and non-dominant upper extremity, consistent with previous results[8,13]. The ulnar nerve at the upper extremity is easily imaged using ultrasound, and no difficulty occurred in locating the landmarks of the cubital tunnel[9]. The abnormal susceptibility of diabetic nerves to compression could be attributable in part to chronic ischemic injuries. The mean CSA of the ulnar nerve in two measuring sites (OCT, GT) in the diabetes mellitus group was greater than in the control group. The histogram shows difference among three groups of data and quantitative analysis (Fig. 2).

Group	Number	Mid-humerus	Inlet of the cubital tunnel	Outlet of the cubital tunnel	Upon the medial epicondyle	6 cm upon the wrist crease	Guyon tunnel
Control group	100	5.60 ± 1.34	6.38 ± 1.38	6.26 ± 1.29	5.87 ± 1.49	5.00 ± 1.26	4.86 ± 1.16
Diabetes mellitus group	60	5.61 ± 1.30$^{\#}$	6.39 ± 1.35#	6.99 ± 1.41*	5.75 ± 1.37$^{\#}$	5.10 ± 1.15$^{\#}$	5.56 ± 1.27*
Diabetic peripheral neuropathy group	40	5.74 ± 1.37$^{\#+}$	7.29 ± 1.56^{*+}	7.58 ± 1.50^{*+}	5.92 ±1.45$^{\#+}$	5.31 ± 1.24$^{\#+}$	5.98 ± 1.45^{*+}
P-value was calculated by one-way ANOVA with post-hoc comparison. * Compared with the CSA of the ulnar nerve in the control group $p < 0.05$. # Compared with the CSA of the ulnar nerve in the control group $p > 0.05$. + Compared with the CSA of the ulnar nerve in the diabetes mellitus group $p > 0.05$.							

Tab. 3. *CSA of ulnar nerve in two sides (mean ± SD) (mm²)*



CSA – cross-sectional area
MH – mid-humerus (midpoint between elbow cresse and axilla)
ICT – inlet of the cubital tunnel
OCT – outlet of the cubbitla tunnel
UME – upon the medial epicondyle
UWR – 6 cm upon the wrist crease
GT – Guyon tunnel
CG – control group
DMG – diabetes mellitus group
DPNG – diabetic peripheral neuropathy group

Fig. 2. *The three groups compared in a histogram*

High-resolution ultrasonography may assess the prevalence of subclinical neuropathy within diabetes mellitus. Ultrasonographic examination of the ulnar nerves can be an alternative or additional diagnostic modality for the evaluation of neuropathies in diabetic patients. The current approach for localizing and assessing the severity of traumatic peripheral nerve injuries involves clinical evaluation and electrodiagnostic studies. However, the ability of these approaches to determine the extent of nerve damage within the first 6 weeks after trauma is limited[14]. High-resolution sonography clearly depicts peripheral nerve size, spaces occupied by lesions and anatomic variants along the entire length of the normative nerve. Ultrasonographic patterns correlate well with histological structures. Normal peripheral nerves have a characteristic echotexture[15]. There are some occlusive disorders in the vasa nervorum and metabolic changes diminishing oxygen liberation by erythrocytes at the capillary blood vessels, and these disturbances lead to endoneural microhypoxia[16].

Polyneuropathy, a frequent complication of diabetes, can be assessed clinically and electrophysiologically[17]. The clinical spectrum of diabetic neuropathy is variable; it may be asymptomatic, but once established as polyneuropathy, it is irreversible[18]. Neither the duration of diabetes mellitus disease nor the age of the subject correlated with the nerve dysfunction[19].

The cross-sectional area of the ulnar nerve in the diabetic peripheral neuropathy group in three measuring sites (ICT, OCT, GT) was larger than that of the control group and the differences in three measuring sites (OCT, GT) between the diabetes mellitus groups and the control group have statistical significance. Cubital tunnel and Guyon tunnel are partially osseous and partially fibrous pipeline. Our experiment showed that the CSA level of the ulnar nerve in the diabetes mellitus group and diabetes peripheral neuropathy in some measuring points (OCT, GT) is greater than that in the normal control group. So our experiments show that diabetic peripheral neuropathy is more likely to develop in osseous pipeline compression. An underlying mass causing nerve entrapment should not be overlooked in diabetic patients since diabetes makes a nerve more vulnerable to compression due to local ischemia and interference with the innate metabolism of the nerve[20,21]. The difference between the diabetes mellitus group and the diabetic peripheral neuropathy group in six sites has no statistical significance. The combination of electromyography and high-frequency ultrasonography can raise the diagnostic rate of diabetic peripheral neuropathy in type 2 diabetes patients who were diagnosed for the first time. Our experiments show that the cubital tunnel is the most common location where the ulnar nerve is compressed around the elbow. The heterogeneous clinical manifestations may be the result of differing reasons for pressure on the ulnar nerve within the cubital tunnel. In diabetes patients with peripheral neuropathy the ulnar nerve area increases in these points, since diabetes makes a nerve more vulnerable to compression due to a microvascular injury causing local ischemia or by interfering with the innate metabolism of the nerve[22]. Due to the metabolic alterations consequent

Control group	Number	Mid-humerus	Inlet of the cubital tunnel	Outlet of the cubital tunnel	Upon the medial epicondyle	6 cm upon the wrist crease	Guyon tunnel
Male	50	5.94 ± 1.38	6.42 ± 1.38	6.30 ± 1.36	6.18 ± 1.49	5.10 ± 1.27	4.80 ± 1.16
Female	50	5.36 ± 1.31	6.35 ± 1.33	6.22 ± 1.30	5.38 ± 1.35	4.90 ± 1.17	4.93 ± 1.29
***P*-value**		0.01	0.64	0.78	0.02	0.75	0.92

P-values < 0.05 were considered statistically significant.

Tab. 4. *Parameters of ultrasound testing between men and women in the control group (mean ± SD) (mm²)*

to abnormal glucose metabolism, the peripheral nerves show both functional impairment and structural changes, even in the preclinical stage, making them more prone to entrapment in anatomically constrained channels[23]. In terms of internal echogenicity the nerves in diabetic peripheral neuropathy were hypoechoic or anechoic in a few measuring sites. High frequency ultrasound may be helpful in the early diagnosis of peripheral neuropathy in diabetic patients. High-resolution ultrasonography has the potential to detect subclinical autonomic nervous system dysfunction which provides a new method and diagnostic basis for the early stage of diabetic neuropathy. The results indicate that high-resolution ultrasonography is a valuable method in qualifying patients for various types of treatment of peripheral neuropathies resulting from compression[24].

The ulnar nerve mean cross-sectional area in two measuring sites (OCT, GT) in the diabetes mellitus group was slightly larger than that of the control group and shows statistical significance. The mean CSA of the nerve in diabetic patients with DPN is greater than that in diabetic patients without DPN at some sites. The CSA of the ulnar nerve in other sites (MH, UME, UWR) revealed no significant differences between the diabetic peripheral neuropathy group and the control group. The internal echo of the nerve in diabetic peripheral neuropathy rendered the boundaries fuzzy. High-resolution ultrasonography may assess the prevalence of subclinical neuropathy within diabetes mellitus. The ulnar nerve cross-sectional area increase may predict early asymptomatic neuropathy. Much of this variability is due to differences in measurement techniques along with the differences between the populations studied. High-resolution sonography is easily available and has the potential to become the first modality for the evaluation of focal peripheral nerve disorders[4]. High-resolution ultrasonography showed significant thickening of the ulnar nerves in patients with diabetic peripheral neuropathy in some measuring sites. High-resolution sonography is useful in characterizing peripheral nerve lesions and can complement other diagnostic investigations such as the nerve conduction study.

Conclusions

In conclusion, there are different characteristics of the ulnar nerve at the different measurement sites. High-resolution ultrasonography may detect early diabetes mellitus with peripheral neuropathy. High-resolution ultrasonography is a valuable modality in the diagnosis of diabetic peripheral neuropathy.

Conflict of interests

The authors do not declare any financial or personal links to other persons or organizations that could adversely affect the content of this publication or claim rights thereto.

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Ethical approval

The experimental protocol was approved by the Institutional Human Study Committee of the Affiliated Hospital of Guizhou Medical University, China.

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