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Original Article

Is ultrasonography useful in the diagnosis of the polyneuropathy in diabetic patients?

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Abstract. [Purpose] The aim of this study was to investigate the usefulness of ultrasonography for the diagnosis of polyneuropathy in diabetic patients by examination of the median and ulnar nerves. [Subjects and Methods] Sixty-three diabetic patients and fourteen controls were enrolled in the study. Nerve conduction studies were performed on both upper and lower limbs. Median and ulnar nerve cross-sectional areas were measured at the wrist and forearm levels in 140 hands by ultrasound. [Results] The median nerve cross-sectional area was increased at the hook of hamatum, pisiform bone, and radioulnar joint levels in patients with carpal tunnel syndrome. The ulnar nerve area at the medial epicondyle was significantly increased in the diabetic polyneuropathy (9.2 ± 1.6), diabetic polyneuropathy plus carpal tunnel syndrome (9.3 ± 1.4), and carpal tunnel syndrome (9.2 ± 1.9) groups compared with the control group (7.7 ± 1.1). In receiver operating characteristics analysis, the cutoff value of the ulnar nerve was 8.5 mm^2 at ulnar epicondyle with 71.4% specificity and 70.4% sensitivity, corresponding to the highest diagnostic accuracy for diabetic polyneuropathy. [Conclusion] Ultrasonographic examination of the median and ulnar nerves can be an alternative or additional diagnostic modality for the evaluation of neuropathies in diabetic patients.
Key words: Polyneuropathy, Ultrasound, Diabetes mellitus

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INTRODUCTION

Diabetic polyneuropathy (DPN) is the most common long-term complication in diabetes mellitus and affects more than 50% of patients[1]. DPN can affect any part of the nervous system (distal, proximal, large, small, motor, or autonomic fibers). Accurate diagnosis of peripheral neuropathies is possible with the use of clinical and electrophysiological tests. Nerve conduction studies (NCSs) are noninvasive, sensitive, and objective procedures[2]. In recent years, due to improved technology, ultrasonography (US) has been regarded as an inexpensive, reproducible, and more comfortable technique, and it can be utilized as an alternative method for detecting neuropathies. However, reports on the use of US for polyneuropathy are limited. Most studies have investigated the 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[3, 4]. On the other hand, Hobson-Webb et al. argued that the cross-sectional area (CSA) of the lower extremity peripheral nerves did not significantly differ between DPN patients and controls[5]. So far, there are no studies that have evaluated the upper extremity nerves at multiple sites in diabetic patients. In this blinded, prospective study, we aimed to investigate the usefulness of US for the diagnosis of polyneuropathy in diabetic patients by investigating the median and ulnar nerves.

SUBJECTS AND METHODS

One hundred seven patients (72 females and 35 males) who had type-2 diabetes mellitus according to the criteria of the American Diabetes Association[6] and were referred to the Physical Medicine and Rehabilitation Electrodiagnosis Laboratory, Marmara University, were enrolled in the present study. Additionally, we recruited 14 healthy age-matched volunteers without diabetes or carpal tunnel syndrome (CTS) as controls. Patients who had thyroid or liver disorders, high blood urea nitrogen, any inflammatory disorder, or any malignancy, those who consumed alcohol, and those who had had a previous carpal tunnel operation were excluded from the study. Patients who complained of ulnar entrapment and those with isolated ulnar nerve entrapment based on electrodiagnostic tests were also excluded. The study protocol was approved by the local ethics committee, and all patients gave written informed consent before participating in the study.

Systemic and neuromuscular examinations (light touch, pinprick, position, temperature, vibration senses, knee and ankle stretch reflexes) were performed by a clinician who was blinded to the results of the nerve conduction studies (NCSs) and US. According to a literature search, no gold standard for the diagnosis of CTS and DPN has been established; therefore, we used clinical evaluation and electrophysiological findings for the diagnosis. For clinical DPN, a scoring system was used based on a previous study[7], and the patients were defined as with or without DPN. A Katz hand diagram was used for clinical CTS[8, 9]. NCSs were performed with conventional procedures and a standard device (Medtronic-Keypoint, Denmark, 2007) by the same physician, who was blinded to the clinical assessment. All studies were performed at standard room temperature 25 °C. For the motor NCSs of the median, ulnar, peroneal, and tibial nerves and second lumbrical-interosseous muscle median-ulnar distal latency (LIMULD), differences were measured. The compound muscle action potential (CMAP) was recorded with surface electrodes from the abductor pollicis brevis muscle for the median nerve, the abductor digiti minimi muscle for the ulnar nerve, the abductor hallucis longus muscle for the tibial nerve, and the extensor digitorum brevis muscle for the peroneal nerve with a standard distance of 8 cm. For the sensory NCSs, the median, ulnar, and sural nerves were measured. Sensory NCSs were recorded using cup electrodes from the third digit antidromically with a standard distance of 14 cm for the median nerve, from the fifth digit with a standard distance of 12 cm for the ulnar nerve, from the first digit with a standard distance of 9 cm for the radial nerve, and from the midpoint of the calf 14 cm from the lateral malleolus for the sural nerve. For LIMULD, median and ulnar motor NCSs were recorded from the second lumbrical-interosseous muscle with a standard distance of 9 cm for the median and ulnar nerves. The average reference values for the nerve conduction velocities (NCVs) in our laboratory are 50 m/s for the median and ulnar motor NCVs and 40 m/s for the tibial and peroneal motor NCVs. Electrophysiological diagnoses of CTS and DPN were obtained according to the normative values established in our laboratory. Values of greater than 3.7 ms for median motor nerve distal latency and median sensory nerve velocity, slower than 50 m/s for the wrist-third digit segment, and more than 0.4 ms for LIMULD were considered to indicate median nerve demyelination[10]. Subjects with abnormal electrodiagnostic results in one or more nerves in the upper limbs, in addition to the median nerve and one or more nerves in the lower limbs, were considered to have DPN. The electrophysiological testing was extended if a suspicious condition, such as ulnar neuropathy and radiculopathy, was present. Patients with any other neuropathic findings, such as isolated ulnar nerve entrapment or radiculopathy, were excluded from the statistical analysis. Finally, patients were classified into four groups according to electrophysiological diagnosis: normal, CTS, DPN, or CTS in the background of DPN (DPN+CTS).

Sonographic examinations were performed with a 6–18 MHz linear array probe (Mylab Esaote, Genoa, Italy) by a well-trained specialist who was blinded to the participant's history and NCS results. All examinations were performed with the participants in a supine position on a table. Nerve CSAs were measured at various levels: the hook of hamate (MHAM), pisiform bone (MPSI), radioulnar joint (MRUE), distal one-third of the forearm (MDIS), proximal one-third of the forearm (MPROX), and medial epicondyle (MEPI) for the median nerve, and the radioulnar joint (URUE), distal one-third of the forearm (UDIS), proximal one-third of the forearm (UPROX), and medial epicondyle (UEPI) for the ulnar nerve. 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. A CSA of the median nerve greater than 10 mm^2 at the pisiform level was used for sonographic diagnosis of CTS in accordance with the literature and our laboratory values[11, 12].

Statistical analyses were performed using the Statistical Package for the Social Sciences software (11.5.0.SPSS version 11.5.0). Categorical values (gender, duration of diabetes, and clinical scores) were analyzed using χ^2 tests. To correlate US findings with other parameters, the Pearson correlation coefficient and ANOVA tests were used. To assess the optimal possible cut-off values of sonographic nerve CSAs for the diagnosis of DPN, receiver operating characteristics (ROC) curves were used. P-values less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 140 hands (28 control, 24 normal, 34 CTS, 26 DPN, 28 DPN+CTS) of 63 patients and 14 control subjects were included in the analysis (mean ages of 47.6 ± 13.1, 43.1 ± 11.7, 50.3 ± 8.01, 51.4 ± 12.5, and 59.1 ± 5.04, respectively). In diabetic patients, eight hands were excluded based on ulnar entrapment findings, and six hands were excluded based on radiculopathy.

Table 1. Mean CSAs of the median nerve

	Control (n=28)	Normal (n=24)	CTS (n=34)	DPN (n=26)	DPN+CTS (n=28)
MRUE (mm^2)	8.9 ± 1.7	9.7 ± 1.8	14.5 ± 5.1*	10.8 ± 1.9	12.5 ± 2.6*
MPSI (mm^2)	8.8 ± 1.3	9.2 ± 1.7	14.4 ± 4.7*	10.5 ± 2.3	12.5 ± 3.3*
MHAM (mm^2)	9 ± 1.3	8.8 ± 1.8	12.9 ± 3.4*	10.3 ± 2.7	11.5 ± 2.6*
MDIS (mm^2)	6 ± 1.1	7.3 ± 1.5	7.02 ± 1.4	7.5 ± 2.8*	6.8 ± 1.2
MPROK (mm^2)	5.4 ± 1.1	6.4 ± 1.3	6.2 ± 1.1	6.8 ± 2.3*	6.3 ± 1.4
MEPI (mm^2)	8.7 ± 1.5	9.9 ± 2.1	10.2 ± 2*	10.5 ± 1.8*	10.6 ± 1.8

CSAs: cross-sectional areas; MHAM: median nerve at the hamatum hook; MPSI: median nerve at the pisiform; MRUE: median nerve at the radioulnar joint; MDIS: median nerve at the distal one-third level of the forearm; MPROX: median nerve at the proximal one-third level of the forearm; MEPI: median nerve at the medial epicondyle.
*p<0.05

Table 2. Mean CSAs of the ulnar nerve

	Control (n=28)	Normal (n=24)	CTS (n=34)	DPN (n=26)	DPN+CTS (n=28)
URUE (mm^2)	5.6 ± 0.8	5.5 ± 0.9	6.2 ± 1.6	6.4 ± 1.9	6.2 ± 1
UDIS (mm^2)	5.9 ± 0.8	5.9 ± 1.1	5.6 ± 0.9	6.1 ± 1	6.1 ± 0.8
UPROX (mm^2)	6.1 ± 1	5.9 ± 1.2	5.5 ± 0.9	6.5 ± 1.4*	6 ± 0.9
UEPI (mm^2)	7.7 ± 1.1	8.1 ± 1.6	9.2 ± 1.9*	9.2 ± 1.6*	9.3 ± 1.4*

Post hoc analysis: p=0.014 for DPN vs. CTS at the UPROX; p=0.01, p=0.003, and p=0.002 for DPN vs. control, CTS vs. control, and DPN+CTS vs. control at the UEPI, respectively.
CSAs: cross-sectional areas; URUE: ulnar nerve at the radioulnar joint; UDIS: ulnar nerve at the distal one-third level of the forearm; UPROX: ulnar nerve at the proximal one-third level of the forearm; UEPI: ulnar nerve at the medial epicondyle.
*p<0.05

Table 3. Cutoff values for the UEPI for the diagnosis of DPN

	Cutoff value, mm^2	Sensitivity	Specificity	Area under the ROC curve
UEPI	8.5	70.4	71.4	0.787
UPROX	5.5	75.9	25	0.530
UDIS	5.5	74.1	32.1	0.554
URUE	5.5	75.9	42.9	0.649

UEPI: ulnar nerve at the medial epicondyle; UPROX: ulnar nerve at the proximal one-third level of the forearm; UDIS: ulnar nerve at the distal one-third level of the forearm; URUE: ulnar nerve at the radioulnar joint

There was a significant increase in the median nerve CSA in the CTS and DPN+CTS groups when compared with the control, normal, and DPN groups at the radioulnar joint, pisiform, and hook of hamate hook levels (Table 1). The CSAs of the median nerve at the distal one-third of the forearm and proximal one-third of the forearm levels were higher in the DPN group compared with the control group (p=0.038 and p=0.035). There was a significant increase at the MEPI in the CTS, DPN, and DPN+CTS groups when compared with the control group (Table 1).

There was no statistically significant difference in the ulnar nerve at the radioulnar joint and distal one-third of the forearm levels between the groups. At the UPROX level, there was a significant increase in ulnar nerve CSA in the DPN group (6.5 ± 1.4) compared with the CTS group (5.5 ± 0.9). At the medial epicondyle level, the CSA of the ulnar nerve was significantly smaller in the control group (7.7 ± 1.1) compared with the CTS (9.2 ± 1.9), DPN (9.2 ± 1.6), and DPN+CTS (9.3 ± 1.4) groups (Table 2).

In the ROC analysis, cutoff values of 8.5 mm^2 at the UEPI with 71.4% specificity and 70.4% sensitivity and 5.5 mm^2 at the UPROX, UDIS, and URUE levels with 25%, 32.1%, and 42.9% specificity and 75.9%, 74.1%, and 75.9% sensitivity, respectively, corresponding to the highest diagnostic accuracy for DPN in terms of ulnar nerve CSA (Table 3).

According to the above cutoff values, the most effective sonographic parameter for DPN diagnosis was the CSA at the UEPI. To compare the diagnostic utility of US with NCS, a new sonographic classification was applied to the groups (Table 4).

Table 4. Ultrasonographic classification

Normal: MPSI<10 mm^2 and bilateral UEPI<8.5 mm^2
CTS: MPSI>10 mm^2 and bilateral UEPI<8.5 mm^2
DPN: MPSI<10 mm^2 and bilateral UEPI>8.5 mm^2
DPN+CTS: MPSI>10 mm^2 and bilateral UEPI>8.5 mm^2

CTS: carpal tunnel syndrome; DPN: diabetic polyneuropathy; MPSI: median nerve at the pisiform; UEPI: ulnarnerve at the medial epicondyle

DISCUSSION

In this study, the CSAs of the ulnar nerve were larger at epicondyle level in the patients with diabetic polyneuropathy. Additionally, median nerve CSAs were larger in diabetic patients with carpal tunnel syndrome at wrist levels compared with those of the healthy controls.

Diabetic distal symmetrical sensorimotor polyneuropathy is the most common form of neuropathy in diabetic patients and can cause many serious complications such as diabetic foot, Charcot joint, and flexion contractures, which reduce quality of life[13]. Upper limb symptoms are often associated with proximal spreading of the DPN; however, these symptoms can be observed in other or adjunctive entrapment neuropathy components such as CTS and ulnar neuropathy at the elbow.

CTS is the most common entrapment neuropathy in diabetic patients[14]. A previous study showed that the LIMULD difference can help to detect CTS in the background of DPN in NCSs[10]. Conversely, US has been used for the diagnosis of entrapment neuropathies such as CTS and DPN[11, 15–17]. Wong et al.[15] demonstrated that a median nerve CSA greater than 9.8 mm^2 supports a diagnosis of CTS with 89% sensitivity and 83% specificity. Additionally, El-Miedany et al.[11] suggested that a median nerve CSA of 10 mm^2 confirms a diagnosis of CTS with 97.9% sensitivity and 100% specificity. Watanabe et al.[3, 4] showed that the median nerve (at the wrist) and tibial nerve (at the ankle) CSAs were increased in diabetic patients when compared with their control group and that CSAs were negatively correlated with motor nerve conduction velocity.

In our study, we found a significant increase in the median nerve CSA at the epicondyle level in the CTS (10.1 ± 2), DPN (10.2 ± 2), and DPN+CTS (10.6 ± 1.7) groups when compared with the control group (8.7 ± 1.5). Additionally, the median nerve CSA was greater at wrist levels than in the control and DPN groups if there was CTS with or without DPN. These results support the finding that the median nerve enlarges at the wrist in carpal tunnel syndrome, as reported in previous studies. In another study, Chen et al.[17] compared median nerve CSAs among diabetic patients with CTS and DPN+CTS. They found greater CSAs at the wrist and in the carpal tunnel in the latter group. However, median nerve CSAs are not helpful in the diagnosis of polyneuropathy, and they do not discriminate CTS in the background of DPN according to our results.

The US features of ulnar nerve CSAs have not been systematically studied to a sufficient extent in diabetic patients. In a study of 98 patients with DPN and 90 controls, the median and ulnar nerve CSAs were found to be increased in demyelinating neuropathies[18]. Arumugam et al.[19] compared patients with DPN with normal controls and found that ulnar nerve CSAs were significantly increased (p=0.016) at the level of mid-forearm. The ulnar nerve may become enlarged at the elbow due to structures that pressure the nerve (ganglia, anconeus epitrochlearis muscles, etc.), and this can lead to nerve entrapment. Furthermore, in addition to entrapment, peripheral nerve thickening can occur as a result of thickening of capillary walls in the endoneurium and increased intracellular hydration due to increased sorbitol in diabetic patients[20, 21]. To minimize the effect of local nerve entrapment, clinical and electrophysiological exclusion was performed. In the current study, we measured the ulnar nerve from four regions. We found increased CSAs at the epicondyle level in the DPN and DPN+CTS groups and as an interesting finding in CTS patients with diabetes mellitus when compared with the control group. These results showing that electrophysiological CTS can be a part of the polyneuropathy in diabetic patients should be interpreted carefully. Kim et al.[22] also found increased CSAs of the median nerve in DPN-only patients compared with those of healthy controls at the wrist. Therefore, ultrasonographic CTS diagnoses are inconsistent with electrophysiological results in patients with DPN. However, they did not examine the ulnar nerve. The current diagnostic criteria for CTS, DPN, and DPN+CTS should be reconsidered. It appears that, clinical, electrophysiological, and ultrasonographic diagnoses should be confirmed with a new gold standard technique by further studies with a larger population.

The cutoff values derived from ROC analysis and an ulnar CSA greater than 8.5 mm^2 at the epicondyle level supported the diagnosis of DPN with 70.4% sensitivity and 71.4% specificity in our study. Ulnar nerve entrapment is the second most common entrapment neuropathy in diabetic patients[23]. The usefulness of US in diagnosis of ulnar nerve entrapment was not examined in this study; thus, these cutoff values patients who had clinical or electrodiagnostic ulnar nerve entrapment were excluded. In view of this cutoff and the literature, a sonographic classification can be done according to ulnar nerve CSAs at the medial epicondyle and median nerve CSAs at the wrist (Table 4).

According to our results, four normal subjects were diagnosed as CTS and five normal subjects were diagnosed as DPN by using US. Two possible reasons for these results are as follows: these patients might have had CTS or DPN but were electrophysiologically normal, or US might have exhibited some degree of false-positive results.

The most important limitation of our study was that focal entrapment neuropathies might have been confused with DPN because they cannot be distinguished accurately. This bias was minimized by use of blinded researchers and standardized protocols.

In conclusion, neither US nor NCSs are a gold standard for the evaluation of peripheral nerves. NCS reflects nerve function better than US and provides valuable information for differential diagnosis. US is a more comfortable technique for the patient and provides a dynamic evaluation. Increased CSAs of the ulnar nerve at the medial epicondyle level can be useful for the diagnosis of DPN, particularly for screening. In general, the relationship between generalized neuropathy and focal entrapment neuropathies is complex and difficult to clarify. We suggest that the combination of US and NCS may be used for the diagnosis of neuropathies in diabetic patients.

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