Original Article

Assessment of peripheral neuropathy in type 2 diabetes by diffusion tensor imaging

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Background: To evaluate the diagnostic accuracy of diffusion tensor imaging (DTI) in diabetic peripheral neuropathy (DPN) for patients with type 2 diabetes and detect the correlations with electrophysiology.

Methods: A total of 27 patients with type 2 diabetes with DPN, 24 patients with type 2 diabetes without peripheral neuropathy (NDPN), as well as 32 healthy controls (HC) were enrolled in this study. Clinical examinations and neurophysiologic tests were used to determine the presence of DPN. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of peripheral nerves, including the tibial nerve (TN) and common peroneal nerve (CPN), were calculated. Receiver operating characteristic (ROC) analysis was performed for FA and ADC values. Pearson's correlation coefficient was used to assess the correlation between DTI and electrophysiology parameters in the patient group.

Results: The tibial and common peroneal nerve FAs were lowest (P=0.003, 0.001, respectively) and ADC was highest (P=0.004, 0.005, respectively) in the DPN group. The FA value of the axonal injury group was lower than that in the demyelination group (P=0.035, 0.01, respectively), while the ADC value was higher (P=0.02, 0.01, respectively). In the DPN group, FA value was positively correlated with motor conduction velocity (MCV) (tibial nerve: r=0.420, P=0.007; common peroneal nerve: r=0.581, P<0.001) and motor amplitude (MA) (tibial nerve: r=0.623, P<0.001; common peroneal nerve: r=0.513; P=0.001), while ADC values was negatively correlated with MCV (tibial nerve: r=–0.320, P=0.044; common peroneal nerve: r=–0.569; P<0.001), and MA (tibial nerve: r=–0.491, P=0.001; common peroneal nerve: r=–0.524; P=0.001).

Conclusions: With a lower FA value and higher ADC value, DTI accurately discriminated DPN. The DTI multi-parameter quantitative analysis of peripheral nerves differentiated DPN axonal injury from the demyelinating lesion, and hence, could be applied in the diagnosis of DPN.

Keywords: Diffusion tensor imaging (DTI); peripheral neuropathy; electromyography

Submitted Jan 29, 2021. Accepted for publication Jun 18, 2021.
doi: 10.21037/qims-21-126
View this article at: https://dx.doi.org/10.21037/qims-21-126

Introduction

The accumulating incidence of diabetes foretells the growing complications of diabetic peripheral neuropathy (DPN) (1,2). As one of the most common and complex complications of diabetes, DPN affects >50% of individuals with diabetes (3). Currently, the clinical diagnosis of DPN depends on the clinical sum of diabetes history, clinical manifestations, and physical examination; however, the exact diagnosis of DPN still relies on nerve conduction function examination, quantitative sensory examination, and sural nerve biopsy (4). It can be divided into myelin prolapse and/or axonal injury according to the severity of the lesion, in which decreased motor conduction velocity (MCV) indicates a demyelinating lesion of peripheral nerves. In contrast, a decrease in both MCV and motor amplitude (MA) indicates axonal injury. Axonal injury is a severe complication of DPN, and the impairment of axon continuity can lead to loss of sensory and motor functions of the peripheral nerves. Clinically, the treatment of peripheral neuropathy is evaluated according to the type of nerve injury in order to substantiate the clinical diagnosis and treatment plan. Therefore, distinguishing the type of injury for devising clinical treatment is essential. However, traditional examination methods are time-consuming, invasive, and prone to being affected by various factors. For example, if the peripheral nerves have already suffered irreversible damage, abnormalities will appear in the above examination. Therefore, in terms of the diagnosis of DPN, sensitive techniques are urgently needed.

In recent years, with the development of imaging technology, magnetic resonance imaging (MRI) peripheral neuroimaging is increasingly used to diagnose and evaluate peripheral neuropathy. Magnetic resonance peripheral neuroimaging with a high spatial resolution is a major tool for examining peripheral nerve injury (5-7). Diffusion tensor imaging (DTI) is a new functional MRI technique developed based on diffusion-weighted imaging, which utilizes the anisotropy of water molecule diffusion in tissues to detect the microstructure of the tissues (8). The morphology, structure, and shape of nerve fibers are displayed by DTI (9). There has been extensive use of DTI to diagnose central nervous system (CNS) disorders, including CNS tumors, psychiatric and cognitive disorders, neurodegenerative and demyelinating conditions, epilepsy, and multiple sclerosis. In recent years, the potential for DTI use has expanded to peripheral neuroimaging like inflammatory neuropathies, peripheral nerve tumors, and so on (10,11). Skorpil *et al.* reported that in imaging of the peripheral nervous system, DTI could feasibly evaluate the sciatic nerves of healthy volunteers (12). Hiltunen *et al.* subsequently revealed the potential application of DTI in peripheral nerves at the wrist, knee, and ankle (13). The focus of DTI in evaluating the peripheral nervous system has been in assessing the median nerve at the wrist, with limited reports regarding the performance of DTI at other peripheral sites. Recently, Vaeggemose *et al.* reported their assessment of the technique in imaging peripheral nerves due to polyneuropathy in patients with type 2 diabetes (14).

The 2 DTI parameters, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) are measured to evaluate the integrity of tissue structure and pathological changes. Thus, the present study aimed to investigate whether the DTI method could be applied to detect DPN in patients with type 2 diabetes and analyze the correlation between FA, ADC value, and neuroelectrophysiological examination parameters.

Methods

Study population

The study was conducted following the Declaration of Helsinki (as revised in 2013). The Medical Ethics Committee approved this study of the First Affiliated Hospital of Soochow University (2020-008, Soochow, China). All participants provided informed consent. Among type 2 diabetic patients, we recruited 27 DPN patients whose diagnosis had been confirmed by neuroelectrophysiological testing (15 cases of demyelinating nerve lesion and 12 cases of axonal injury according to neuroelectrophysiological tests) and 24 non-diabetic peripheral neuropathy (NDPN) patients who had diabetes but not associated with peripheral neuropathy from the Department of Endocrinology of our hospital. Moreover, 32 healthy control (HC) volunteers who were age- and gender-matched were recruited by public announcement. All participants were recruited between August 2018 and December 2018. The exclusion criteria were as follows: lower-limb vascular lesions, trauma history or surgical history, acute or chronic musculoskeletal disorders, history of neurotoxin exposure, other neuropathies such as Guillain-Barre syndrome, pain in the nerves of the lower extremities caused by disc herniation, severe cardiac or lung disease, and contraindications to MRI.

Electrophysiological examination and nerve conduction test

We detected DPN based on clinical examination combined with neurophysiologic testing. Neurophysiologic tests were performed using conventional surface electromyography (EMG) examination and nerve conduction tests performed at the right knee joint for the tibial nerve and common peroneal nerve. The values of MA and MCV were determined. Decreased MCV was an indicator for DPN diagnosis with the peripheral demyelinating lesion, while DPN with axonal injury was diagnosed when decreased MA accompanied MCV reduction.

MR neurography

A 12-channel knee coil at a 3T MR system (MAGNETOM Verio, Siemens Healthineers, Erlangen, Germany) was used to conduct MRI. The scanned area ranged from the large trochanter of the femur to the head of the fibula, including the lower part of the sciatic nerve to the common peroneal nerve (CPN) at the head of the fibula. The detailed MR protocol was as follows:

(I) 2D axial T1-weighted imaging (T1WI) scanning parameters were as follows: repetition time/time to echo (TR/TE) =1,318/12.3 ms, field of view (FOV) =150×150 mm^2, matrix size =384×80, slice thickness =3.5 mm, slice gap =0.35 mm, and 48 slices. Scan time =5 min 49 s.

(II) 2D axial T2-weighted imaging (T2WI) scanning parameters were as follows: TR/TE =5,126/86.3 ms, FOV =150×150 mm^2, matrix size =384×80, slice thickness =3.5 mm, slice gap =0.35 mm, and 48 slices. Scan time =3 min 56 s.

(III) The parameters of 2D axial T2W with a fat suppression (FS) pulse were as follows: TR/TE =4,415/75.1 ms, FOV =150×150 mm^2, matrix size =272×100, slice thickness =3.5 mm, slice gap =0.35 mm, and 48 slices. Scan time =4 min 52 s.

(IV) Axial DTI scanning parameters were as follows: TR/TE =4,000/92 ms, FOV =160×160 mm^2, matrix size =128×128, gradient directions =24, slice thickness =3.5 mm, slice gap =30%, b =0, 1,000 s/mm^2. Scan time =17 min 10 s.

Imaging processing

The original images were transmitted to the Siemens workstation. The image of DTI sequence processing and analysis was obtained in the joint neural post-processing software. Then, the DTI image was fused with the T1W sequence to generate the FA and ADC images. As the tibial and peroneal portions of the sciatic nerve at thigh level are separated by a variable amount of fatty connective tissue, we restricted the analysis to the tibial portion of the sciatic nerve to confine the measurement to that of true nervous tissue. Mean values were calculated for each participant as an average of all analyzed nerves.

The region of interest (ROI) was placed at the level of the starting position of the tibial nerve and common peroneal nerve. The ROI was intended to encompass the entire nerve area but not exceed the nerve boundary. The system automatically measured the FA and ADC value of the nerve 3 times and took the average value of the measured data.

Statistical analysis

For the MRI and DTI analyses, 2 radiologists (with 8 and 5 years of experience in MRI with precise anatomical knowledge) independently measured the FA and ADC value. They also observed the changes in the morphology and signaled intensity of CPN and TN on T2WI. All values were depicted as mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was applied to compare the clinical data between groups. Pearson's rank correlation test was used to analyze the correlation between FA, ADC values, and MCV and the motion amplitude of NDPN and DPN groups. The difference between axonal injury and demyelination in the DPN group was analyzed by the Levene test and independent-sample *t*-test. A 2-sided P value <0.05 was defined as statistically significant. The receiver operating characteristic (ROC) was used to assess the efficiency of DTI parameters for diagnostic DPN. In addition, the sensitivity and specificity of the diagnostic threshold were recorded. Statistical analyses were performed using SPSS 21.0 software (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics

The clinical and demographic results are presented in *Table 1*. A total of 83 participants, including 39 males and 44 females, were classified into 3 groups: 27 types 2 diabetic patients with DPN, 24 NDPN patients, and 32

Table 1 Clinical data, nerve conduction studies of TN and CPN between DPN, NDPN, and HC group

Clinical data	HC	NDPN	DPN
N	32	24	27
Age (years)	56.95±7.99	60.5±8.69	56.75±8.26
Male, n (%)	17 (53.1)	11 (45.8)	11 (40.7)
BMI (kg/m^2)	24.6±2.6	25.7±2.3	25.6±2.8
Diabetes duration (years)	–	12.5±8.5	12.1±6.6
HbA1c (%)	–	7.3±1	9.4±2.9
Tibial MCV	–	49.66±5.22	35.28±3.27
Peroneal MCV	–	55.01±1.95	39.27±5.65
Tibial MA	–	5.46±1.75	3.37±2.49
Peroneal MA	–	4.82±2.11	2.42±1.81

TN, tibial nerve; CPN, common peroneal nerve; DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy; HC, healthy control; BMI, body mass index; MCV, motor nerve conduction velocity; MA, motor amplitude.

HCs who were age- and gender-matched. The median age of the participants in the cohort was similar (mean ± SD: 56.95±7.99, 60.5±8.69, 56.75±8.26 in HC, NDPN, and DPN groups, respectively), which increased the accuracy of this study.

MR signal analysis

The ROI was placed at the level of the starting position of the tibial nerve and common peroneal nerve, encompassing the entire nerve area, but did not exceed the nerve boundary.

The tibial and common peroneal nerves were found to be oblate on T1W or T2W axial images, with iso-low signal similar to that of the muscle signal, uneven internal signal, and scattered irregular fat signal, surrounded by the low-signal outer membrane of the nerve, while the edge was detected distinctly against the surrounding adipose tissue. The T1W images showed that the boundary of the nerve bundle in the DPN group was fuzzier than that in the HC group, with fat infiltration of the outer membrane of the nerve (*Figure 1A,1B*). The nerve signals of the HC, NDPN and DPN groups were increased gradually in T2W/FS sequence (*Figure 1C-1E*).

Data measurement

We used T1WI anatomical images to locate the TN and the CPN during FA and ADC measurements. An ROI was placed on FA and ADC images (*Figure 2A,2B*) and was as large as possible without exceeding the nerve boundary. The FA value, ADC value, MCV, and MA of the tibial nerve and common peroneal nerve of the 3 groups were measured. Statistical analysis showed that the FA value and the ADC value of the right TN and CPN at the selected measurement level were normally distributed in the 3 groups. However, significant differences were detected in the FA and ADC values of the TN and CPN between the HC, NDPN, and DPN groups (*Tables 2,3*). The ADC values increased gradually, while the FA value decreased gradually (*Figure 3*).

In the patient group (DPN and NDPN participants), the correlation between the DTI parameters (FA value, ADC value) and MCV, MA were analyzed, respectively. The FA values of TN and CPN were positively correlated with MCV and MA of the nerves, while the ADC values of TN and CPN were negatively correlated with MCV and MA of the nerves (*Table 4*).

The ROC curve analysis showed that the FA diagnostic cutoff point for DPN tibial neuropathy and common peroneal neuropathy was 0.386 and 0.391, respectively, with a sensitivity of 85% and 85%, specificity of 92.5% and 82.5%, and area under the ROC curve (AUC) of 0.933 and 0.901, respectively. The diagnostic cutoff point of ADC for DPN tibial neuropathy and common peroneal neuropathy was 1.087 and 1.099 with 80% and 85% sensitivity, 82.5% and 87.5% specificity, and 0.87 and 0.879 AUC, respectively (*Figure 4*).

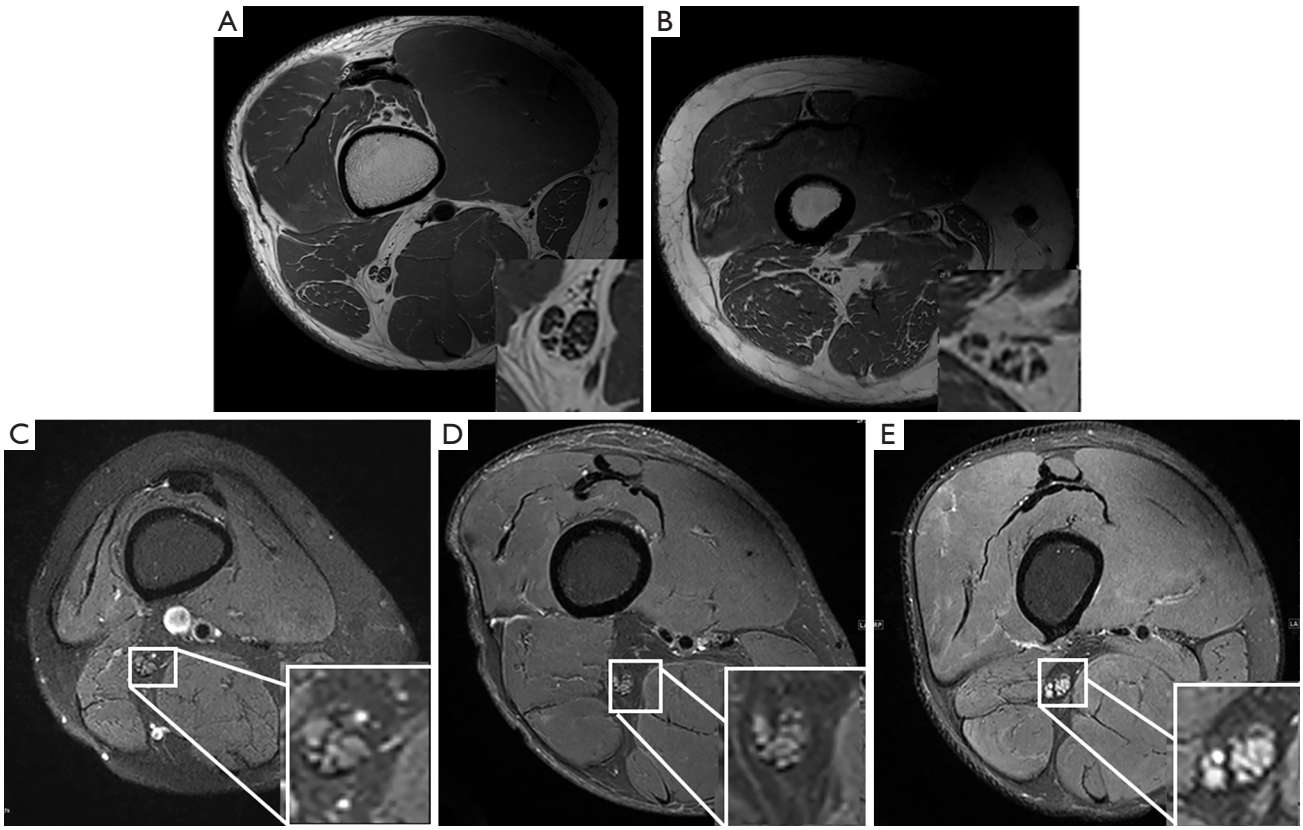

Figure 1 Morphological images of tibial and peroneal nerves. HC group (A) and DPN group (B) images of TN and CPN on T1WI. HC group (C), NDPN group (D), and DPN group (E) images of TN and CPN on T2WI FS. DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy; HC, healthy control; TN, tibial nerve; CPN, common peroneal nerve.

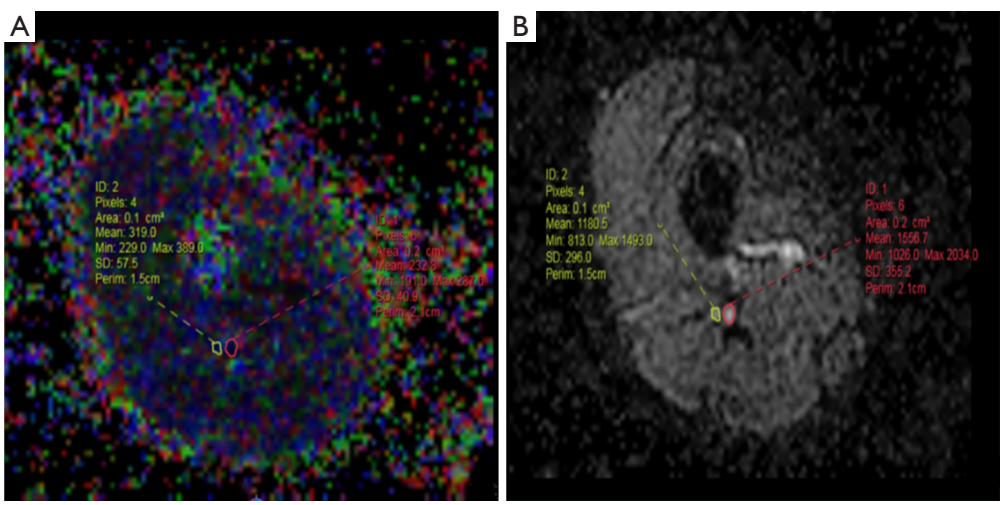

Figure 2 FA and ADC images of TN and CPN. ROI was placed on FA (A) and ADC (B) images for FA and ADC measurements. ROI, region of interest; ADC, apparent diffusion coefficient; FA, fractional anisotropy; TN, tibial nerve; CPN, common peroneal nerve.

Table 2 Statistical analyses of DTI parameters (FA and ADC value) of TN between DPN, NDPN, and HC group

Group	N	FA value	ADC value (10^{-3} mm^2/s)
HC	32	0.45±0.04	0.97±0.08
NDPN	24	0.42±0.03	1.04±0.11
DPN	27	0.36±0.04	1.16±0.09
F value		6.324	5.273
P value		0.003	0.004

One-way ANOVA. Values are mean with corresponding confidence intervals. DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; FA, fractional anisotropy; TN, tibial nerve; DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy; HC, healthy control.

Table 3 Statistical analyses of DTI parameters (FA and ADC value) of CPN between DPN, NDPN, and HC group

Group	N	FA value	ADC value (10^{-3} mm^2/s)
HC	32	0.46±0.03	0.95±0.08
NDPN	24	0.41±0.03	1.01±0.09
DPN	27	0.37±0.04	1.13±0.09
F value		8.653	5.825
P value		0.001	0.005

One-way ANOVA. Values are mean with corresponding confidence intervals. DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; FA, fractional anisotropy; CPN, common peroneal nerve; DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy; HC, healthy control.

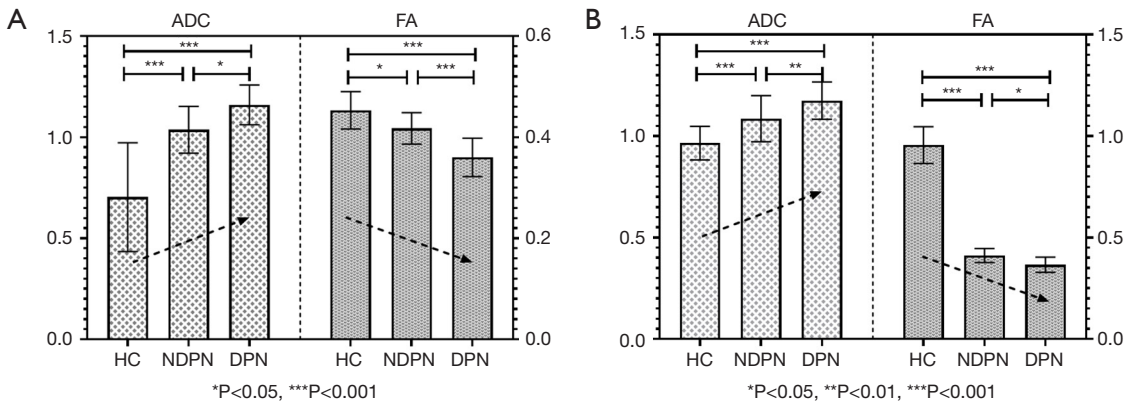

Figure 3 Box-plot results of ADC and FA between HC, NDPN, and DPN groups. ADC value of TN (A) and CPN (B) between groups increased gradually, while FA value decreased gradually. ADC, apparent diffusion coefficient; FA, fractional anisotropy; DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy; HC, healthy control; TN, tibial nerve; CPN, common peroneal nerve.

Table 4 Statistical analyses of the correlation between DTI parameters (FA and ADC value) and MCV, MA in DPN and NDPN groups

	MCV	MA
FA		
TN		
R value	0.420	0.623
P value	0.007	<0.001
CPN		
R value	0.581	0.513
P value	<0.001	0.001
ADC		
TN		
R value	−0.320	−0.491
P value	0.044	0.001
CPN		
R value	−0.569	−0.524
P value	<0.001	0.001

Pearson rank correlation test. R, the correlation coefficient. DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; FA, fractional anisotropy; MCV, motor nerve conduction velocity; MA, motor amplitude; DPN, diabetes with peripheral neuropathy; NDPN, diabetes without peripheral neuropathy.

According to the severity of the lesion, DPN can be divided into demyelination and/or axonal injury, in which decreased MCV indicates peripheral nerve demyelination lesion, while a decrease in both MCV and MA indicates axonal injury. In this study, 15 participants with demyelinating lesions and 12 participants with axonal injury were selected from the DPN group by neuroelectrophysiological examination. In addition, statistically significant differences were noted in the FA and ADC value of the TN and the CPN between the 2 groups (*Tables 5*,*6*). The ADC values of the demyelinating group were lower than those of the axonal injury group, while the FA value was higher. The multiple comparisons are shown in *Figure 5*.

Intra/interobserver statistical analysis showed an excellent agreement of the interobserver and intraobserver performances [with intraclass correlation coefficients (ICCs) of 0.805–0.852 and 0.833–0.903, respectively] in FA. The interobserver performance with ICCs of 0.854–0.973 and the intraobserver performance with ICCs of 0.901–0.963 also exhibited excellent agreement in ADC.

Discussion

This study showed that DTI is a useful tool for discriminating DPN patients with type 2 diabetes, representing an additional non-invasive method for the diagnosis of DPN and enrichment of the clinical diagnosis and treatment program. The complication of DPN is one of the most common long-term complications of diabetes with high mortality and serious adverse effects on quality of life (15-17). Detection and treatment are crucial for the prognosis of DPN. With the development of DTI imaging technology and its wide application in diagnosing CNS diseases, it is increasingly used in the research of peripheral neuropathy (17,18).

The FA value reflects the directional dependence of diffusion of water molecules and the anisotropy of peripheral nerves. In contrast, the ADC value reflects the diffusion magnitude or rate of water molecules, which can be utilized to evaluate the size of the diffusion barrier of the cell membrane or myelin sheath. When the nerve is inflamed or damaged, the ADC value increases. In peripheral neuropathy, axonal degeneration, myelin loss, and Schwann cell necrosis lead to decreased endoneurotic contraction, altering the abovementioned 2 values (18). Some studies have confirmed that DTI technology detects the presence of neuropathy in diabetes, suggesting that it can be used to identify the structural characteristics of neuropathy.

Moreover, a significant decrease of FA values with increased ADC values was detected in patients with severe DPN (19). Consistent with the previous study by Vaeggemose *et al*. using DTI to investigate the lower extremity peripheral neuropathy in diabetic patients, FA value decreased, and ADC value increased in the TNl and CPN between HC, NDPN, and DPN groups. The difference was statistically significant in this study (19). Injury, edema, demyelination, and axonal degeneration of nerves in DPN patients may be the main reasons for FA and ADC values changes. In the early stage of this study, different b values were used to compare the DTI images of the bilateral TN and CPN. It was found that the DTI image with b =1,000 s/mm^2 has a higher score by scoring the display and image artifacts of fiber bundle. Therefore, b =1,000 s/mm^2 was selected to conduct MR examination in this study.

According to MCV and MA, DPN could be divided into demyelinating injury and axonal injury groups. It was found that the FA value of the axonal injury group was

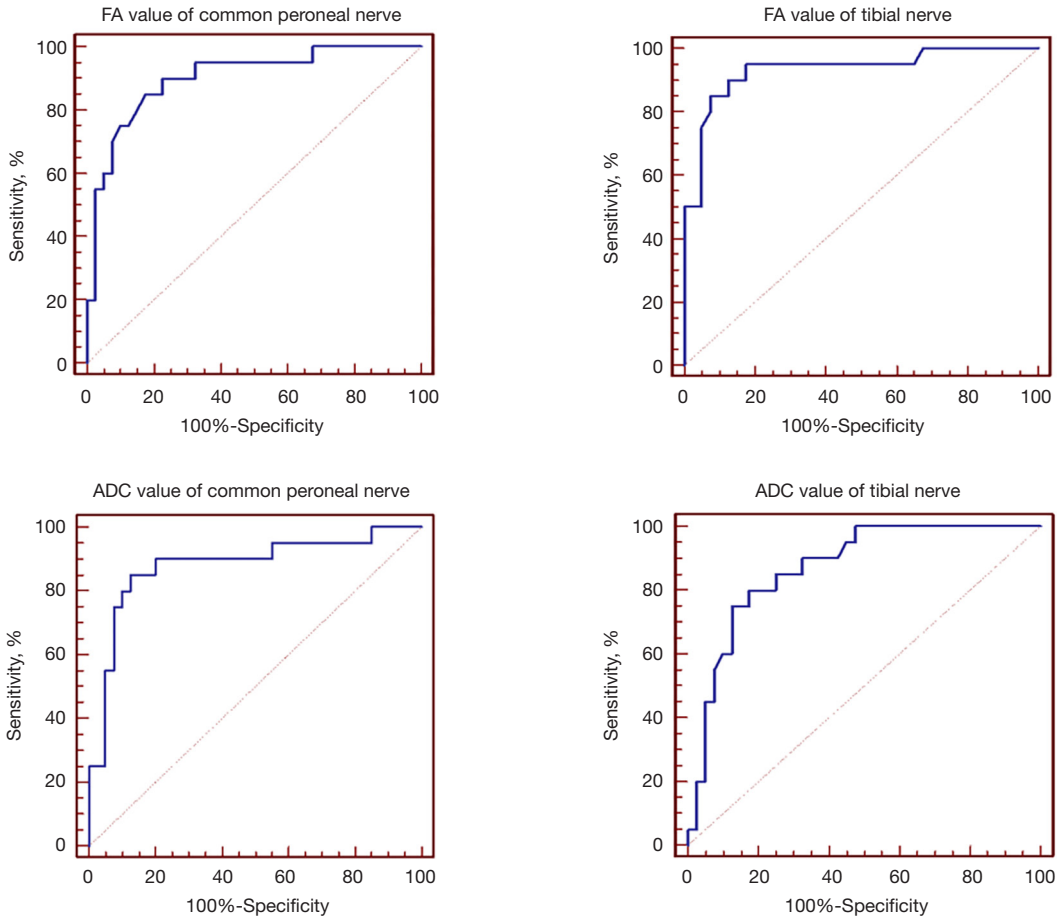

Figure 4 ROC curve of FA and ADC value in diagnosing DPN tibial neuropathy and common peroneal neuropathy. ROI, region of interest; ADC, apparent diffusion coefficient; FA, fractional anisotropy; DPN, diabetes with peripheral neuropathy.

Table 5 Statistical analyses of DTI parameters (FA and ADC value) of TN between demyelinating and axonal injury group

Group	FA value	ADC value (10^{-3} mm^2/s)
Demyelinating (n=15)	0.38±0.03	1.13±0.08
Axonal injury (n=12)	0.34±0.04	1.19±0.11
t value	2.274	–2.442
P value	0.035	0.02

Values are mean ± SD. Independent sample *t*-test. Data were tested by Levene test for homogeneity of variance. DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; FA, fractional anisotropy; TN, tibial nerve.

Table 6 Statistical analyses of DTI parameters (FA and ADC value) of CPN between demyelinating and axonal injury group

Group	FA value	ADC value (10^{-3} mm^2/s)
Demyelinating (n=15)	0.39±0.03	1.11±0.04
Axonal injury (n=12)	0.34±0.03	1.23±0.09
t value	4.12	–4.066
P value	0.01	0.01

Values are mean ± SD. Independent sample *t*-test. Data were tested by Levene test for homogeneity of variance. DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; FA, fractional anisotropy; CPN, common peroneal nerve.

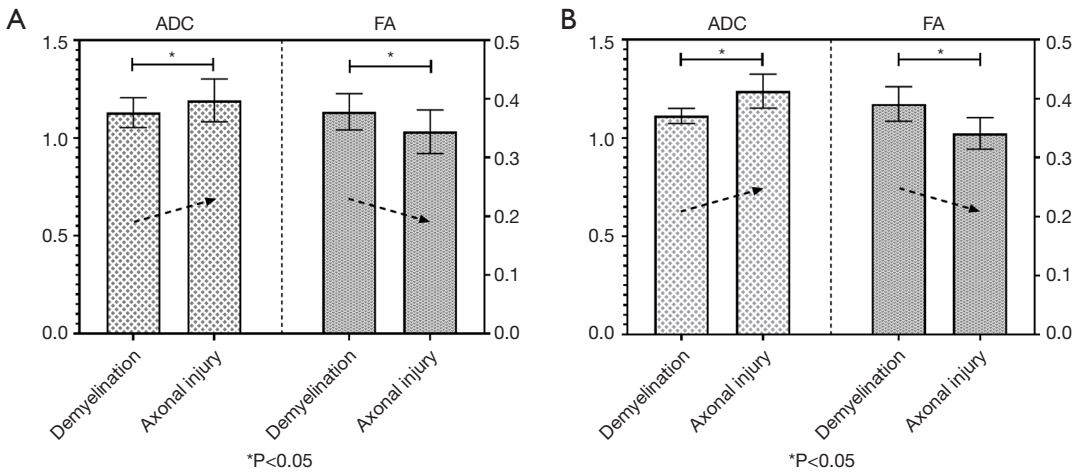

Figure 5 Box-plot results of ADC and FA between axonal injury and demyelinating groups. FA (A) and ADC (B) value of TN and CPN between groups. ADC, apparent diffusion coefficient; FA, fractional anisotropy; TN, tibial nerve; CPN, common peroneal nerve.

significantly lower than that of the demyelinating group, while the ADC value was significantly higher than that of the demyelinating group. This showed that DTI could detect and quantitatively evaluate the development and changes in DPN lesions and the feasibility and reliability of the diagnosis of DPN. Compared to the discomfort induced by EMG examination and the influence of temperature, pH value, electrolyte level, and other factors of EMG examination, DTI examination can observe the morphological changes of peripheral nerves (13,20,21), providing support for the clinical ascertainment of drug injection route and surgical strategy (22,23). In addition, the altered DTI parameter value can be used for the treatment evaluation of peripheral nerves to enrich the clinical diagnosis and treatment program (24).

The ROC curve was used to analyze the sensitivity and specificity of FA and ADC, which could evaluate the diagnostic efficacy of DTI parameters in DPN patients with TN and CPN lesions. The ROC analysis showed that both ADC and FA values were helpful to distinguish patients with DPN from those without DPN. Both ADC and FA values had high sensitivity and specificity. The FA value performed better at identifying DPN patients, which was consistent with previous research (14). Overall, these findings indicated that DTI parameters have good diagnostic efficacy for DPN.

Nevertheless, the present study had several limitations. First, the experimental sample size was small. The older participants had poor compliance, mainly limited by the prolonged scanning time of MRI, rendering it prone to produce motion artifacts and affect image quality. Second, HC participants in this study did not consent to invasive EMG examination. Third, the selection and drawing of the ROI were not devoid of error. Fourth, the number of cases in the DPN group's demyelinating and axonal injury subgroups was relatively small. Thus, the number of cases should be increased in the future for subsequent studies. Furthermore, this was a preliminary study of diffusion imaging technology in DPN diagnosis without showing the distal branches of the TN and CPN, especially the sural nerve that can be biopsied. Thus, in future studies, the sequences might be adjusted to examine the fine nerves, and the accuracy of MRI in diagnosing DPN can be further improved by comparing the findings of the pathological examination.

Conclusions

The value of FA and ADC derived from DTI showed great potential in differentiating the neurological changes in DPN, NDPN patients, and normal individuals. The DTI parameters had good diagnostic efficacy concerning TN and CPN lesions in DPN patients. We found that DTI multi-parameter quantitative analysis of peripheral nerves aids in distinguishing DPN axonal injury from demyelinating lesions. We believe that DTI has potential in the diagnosis and evaluation of DPN.

Acknowledgments

Funding: This work was mainly supported by the program

for Gusu Medical talent of Suzhou city (GSWS2020009), the Translational Research Grant of NCRCH (2020WSB06), National Natural Science Foundation of China (81671743), the Clinical Key Diseases Diagnosis and Therapy Special Project of Health and Family Planning Commission of Suzhou (LCZX201801), the program for Advanced Talents within Six Industries of Jiangsu province (WSW-057), the High-level Health Personnel "Six-One" Project of Jiangsu province in China (LGY2016035), "Science and Education Revitalizing Health" Youth Science and Technology Project of Suzhou (KJXW2020010), and the Technological Innovation Project of Suzhou Jiangsu Province (SYS201734).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-126). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted following the Declaration of Helsinki (as revised in 2013). The Medical Ethics Committee approved this study of the First Affiliated Hospital of Soochow University (2020-008, Soochow, China). All participants provided informed consent.

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Cite this article as: Wang X, Luo L, Xing J, Wang J, Shi B, Li YM, Li YG. Assessment of peripheral neuropathy in type 2 diabetes by diffusion tensor imaging. Quant Imaging Med Surg 2022;12(1):395-405. doi: 10.21037/qims-21-126

