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ORIGINAL ARTICLE

Diffusion tensor imaging in carpal tunnel syndrome

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PURPOSE
We aimed to investigate the efficacy of diffusion tensor imaging in the diagnosis of carpal tunnel syndrome and to obtain a quantitative parameter that may contribute to the diagnosis.

MATERIALS AND METHODS
The median nerves in 57 wrists of 38 patients diagnosed as carpal tunnel syndrome and 30 wrists of 24 normal subjects were prospectively evaluated with a 3T Philips scanner, using standard 8-channel SENSE head coil. Diffusion tensor imaging was performed using spin echo-echo planar imaging. For anatomical reference, a T1-weighted sequence was acquired. Fractional anisotropy and apparent diffusion coefficient measurements were done focally at the carpal tunnel level and from whole median nerve.

RESULTS
In carpal tunnel syndrome patients, both focal carpal tunnel and whole nerve measurements demonstrated statistically significantly lower fractional anisotropy values than normal subjects ($P < 0.001$). No statistically significant difference was observed in apparent diffusion coefficient measurements. The cut-off value obtained by receiver operator characteristics analysis was 0.554 for focal carpal tunnel fractional anisotropy (sensitivity, 80%; specificity, 80%) and 0.660 for whole nerve fractional anisotropy (sensitivity, 82%; specificity, 80%) measurement.

CONCLUSION
Diffusion tensor imaging may contribute to the diagnosis of carpal tunnel syndrome on the basis of fractional anisotropy measurements.

Key words: • *carpal tunnel syndrome* • *diffusion tensor imaging* • *median nerve* • *median neuropathy*

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Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy of an upper extremity, and it is caused by an entrapment of the median nerve at the level of the carpal tunnel (1). The carpal tunnel is formed by the carpal bones, which form a concave arch, and the transverse carpal ligament, which lies on the arch. The ligament is also fused to the pisiform, the hook of the hamate at the ulnar side, the tubercle of the navicular bone, the crest of the trapezium, and the radial styloid (2).

CTS is a common disorder with an estimated 8% annual incidence rate, and an accurate diagnosis can be achieved by considering the patient's electrodiagnostic features and symptom characteristics. Electrodiagnostic testing is considered the single most accurate method of diagnosis, but a high rate of false negatives and positives are also well documented. If electrodiagnostic findings are not available, then the patient's characteristic symptoms and physical examination may provide the best diagnostic information (3).

Fat-saturated, T2-weighted magnetic resonance imaging (MRI) can reveal morphological changes in CTS patients, such as nerve enlargement, nerve flattening, increased nerve signal intensity, and bowing of the flexor retinaculum at the level of the hamate hook. However, the sensitivity and specificity of MRI findings are low; therefore, conventional MRI may provide insufficient diagnostic data for clinically assessing CTS (1).

Diffusion tensor imaging (DTI) is an advanced MRI technique that is used to measure the diffusion of water in tissue (4). In white matter, water diffusion is anisotropic due to its impermeable boundaries, and this anisotropy can be measured with DTI; therefore, its main clinical application is white-matter tract visualization, but recently, it has been shown that DTI can be useful for imaging non-neural tissue, such as peripheral nerves (5–8), muscle (9), and prostate (10). There are a few preliminary reports in the literature on the application of DTI for diagnosis of CTS, but they include a limited number of subjects. Nevertheless, these reports found decreased fractional anisotropy (FA) and increased radial diffusivity at the median nerve within the carpal tunnel (8, 11, 12).

Here, we investigated DTI's diagnostic utility in a large group of CTS patients using two quantitative measures: FA and the apparent diffusion coefficient (ADC). We also measured the correlation between CTS severity and FA.

Materials and methods

Patients

We prospectively evaluated 57 wrists in 38 CTS patients (34 females and 4 males; mean age, 48 years; age range, 25–73 years; median age,

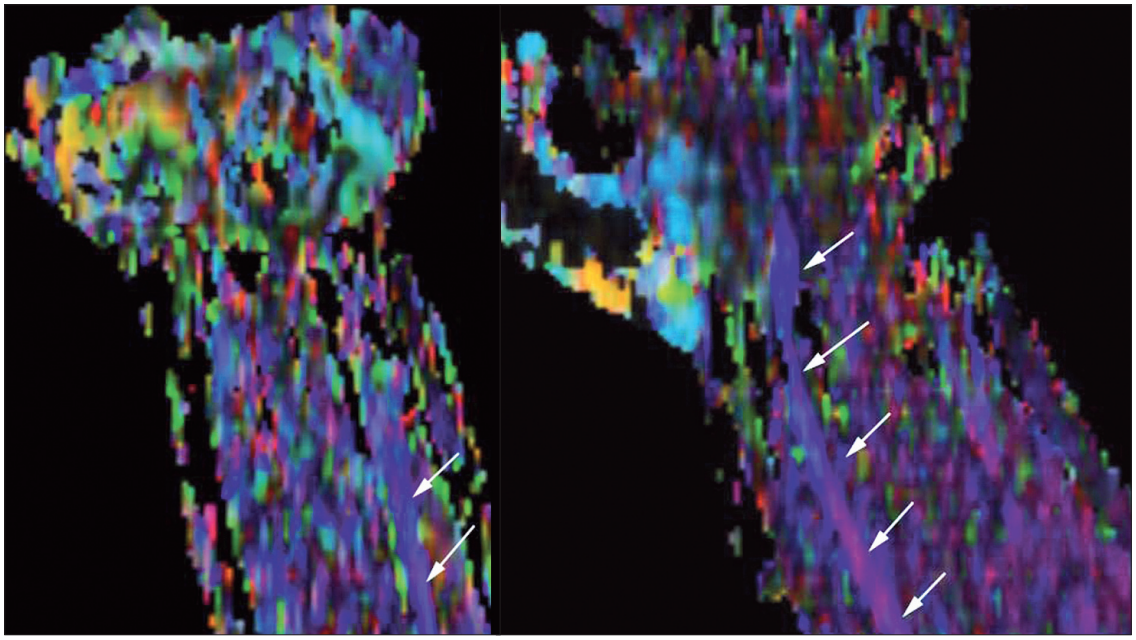

Figure 1. A color-coded map of the coronal plane that shows the median nerve in a CTS patient *(arrows)*.

47 years; interquartile age range, 43–56 years). Regarding the wrists, 19 patients had bilateral and 19 patients had unilateral involvement. To be included in the study, a pathological median nerve conduction test was required; exclusion criteria were contraindications for MRI, including a history of neuromuscular disorder, a history of surgery on the involved median nerve, or pregnancy.

The primary control group included 30 wrists in 26 subjects (17 females and 9 males; mean age, 34 years; age range, 21–68 years; median age, 30 years; interquartile age range, 26–34 years). From this larger group, a smaller age-matched control group was constructed because a previous study suggested that the median nerve might be susceptible to age-related FA and ADC changes (8). The age-matched group included 10 subjects (7 females and 3 males; mean age, 46 years; range, 30–68 years; median age, 42 years; interquartile range, 32–60 years). The control group had no CTS symptoms, as determined by negative Phalen's test result, and no history of wrist surgery. The study was approved by Yeditepe University Institutional Review Board, and all subjects provided informed consent before the MRI exam.

Patients were recruited from three centers, and the CTS diagnosis was based on clinical symptoms and electrophysiological test results; a sensorial-nerve conduction velocity across the wrist that was slower than 45 m/s and/or a motor-distal conduction latency longer than 4 ms resulted in a diagnosis of CTS. Electrophysiological test results were also used to categorize CTS severity; mild CTS consisted of slowed sensorial-nerve conduction, whereas severe CTS consisted of slowed motor-distal conduction in addition to slowed sensorial-nerve conduction.

MRI technique

MRI was performed on a 3T MRI system (Intera Achieva, Philips Medical Systems, Best, the Netherlands) with a maximum gradient amplitude of 30 mT/m, a 150 T/m/s slew rate, and an 8-channel head coil. The coil was positioned at the magnet's isocenter, and the subjects were scanned in a prone position with their hands over their head within the coil, and they were immobilized with cushions, sandbags, and bandages.

A single-shot spin-echo, echo-planar DTI sequence was used with the following parameters: TR/TE, 4.600/90 ms; flip angle, 90°; field of view, 140 mm; matrix size, 128×128 mm; and number of signals averaged, 3. Diffusion weighting (b value=1000 s/mm^2) was applied in 16 directions, and the total sequence duration was 7 min and 49 s. Data were acquired in 35 axial slices that were with no 4 mm thick gap between slices. The subject's detailed anatomy was imaged with a T1-weighted axial sequence that had the following parameters: TR/TE, 382/20 ms; flip angle, 90°; field of view, 140 mm; and number of signals averaged, 2.

Post-processing and quantitative DTI evaluation

After DTI data were transferred to a workstation, manufacturer-supplied software (PRIDE, Philips Medical Systems, Best, the Netherlands) was used for measurements and fiber tracking. Tractography was performed, in consensus, by a radiologist and a radiology technician who is experienced in DTI post-processing. First, color-coded maps in the coronal plane was used to locate the nerve (Fig. 1). Second, circular regions of interests (ROIs) were placed in the anatomic location of the median nerve expected on the basis of information from coronal and axial color-coded maps (Fig. 2a and 2b). ROI placement was done at two levels: the distal radioulnar joint and the forearm level. The locations of the ROIs were confirmed by using the anatomical information on the T1-weighted reference (Fig. 2c). Third, the tracts were obtained automatically by the software after accurate replacement of the ROIs (Fig. 2d). The tracts were also confirmed on the coronal and axial T1 views (Fig. 3). Fourth, quantitative measurements were taken. Whole median nerve measurements were made on the coded whole tract. After flexor

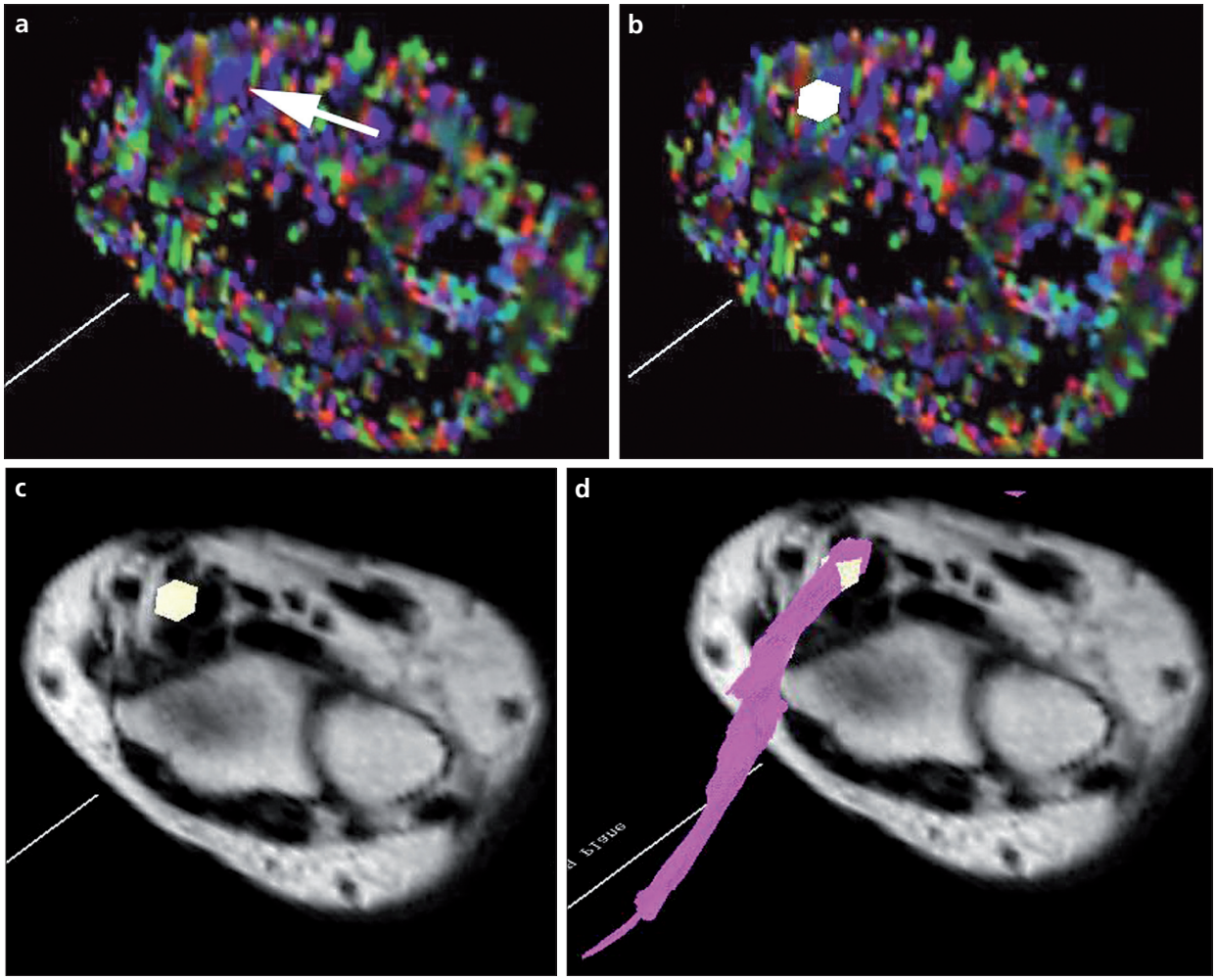

Figure 2. a–d. The steps of the tractography method. The median nerve (*arrow*) is localized on axial color-coded maps **(a)**. After placing the region of interest **(b)** and confirming it on the T1 reference images **(c)**, the median nerve tract was automatically traced by computer software **(d)**.

retinaculum level was determined on the tract, focal carpal tunnel measurements were done on this tract by using a smaller ROI than the nerve to avoid partial volume effects. For the quantitative assessment of the data, two parameters (FA and ADC), which were automatically calculated by the software, were used.

Statistical analysis

Statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 18, SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to confirm that quantitative data were normally distributed. The Student's t-test was used to compare the FA and ADC values of the primary control group and CTS patients, and then the Mann-Whitney U-test was used to replicate this analysis using the

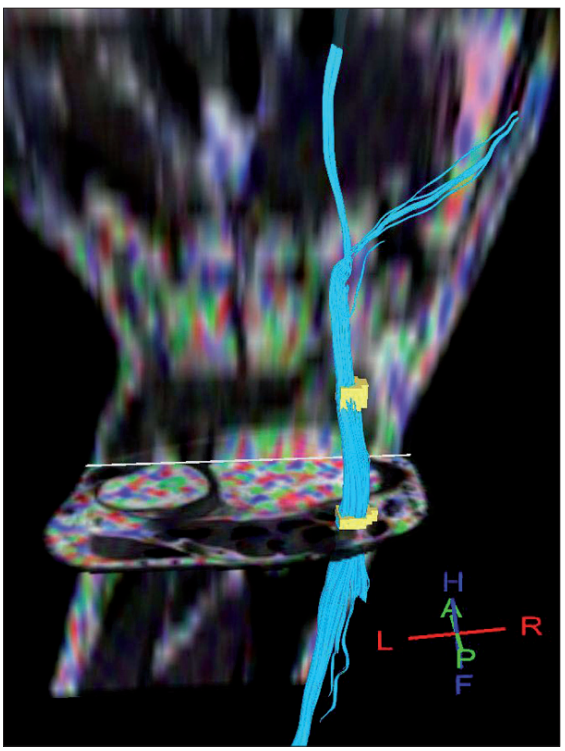

Figure 3. The final median nerve tract of a CTS patient, which was confirmed using coronal and axial T1 images. Whole and focal median nerve measurements were then made on this tract.

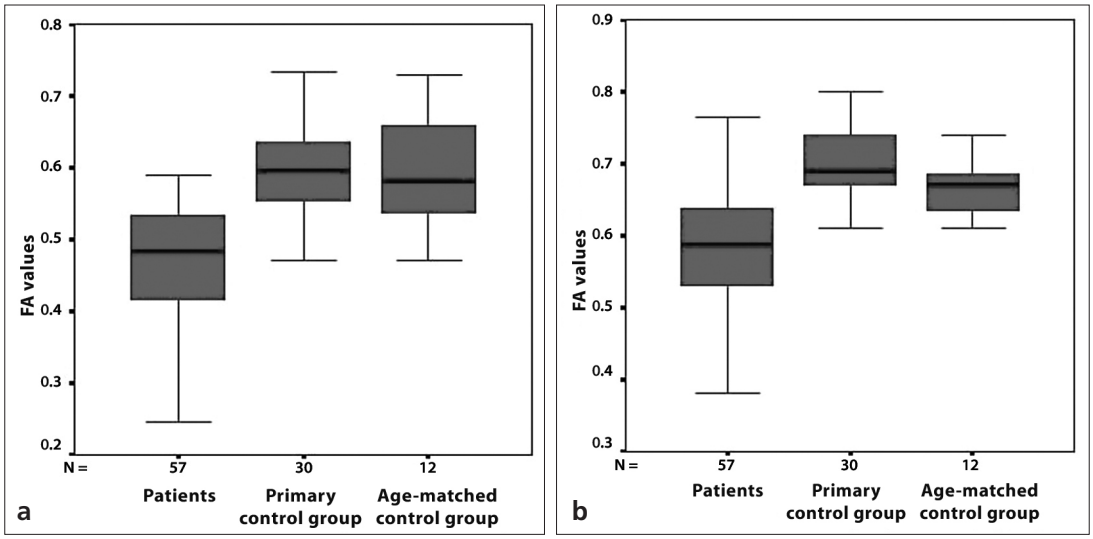

Figure 4. a, b. Box-and-whisker plots demonstrating the median (*middle line of the box*), quartiles (*the top and bottom lines of the box*), the upper extreme value (*upper whisker*) and the lower extreme value (*lower whisker*) of fractional anisotropy (FA) values in **(a)** focal carpal tunnel measurements and **(b)** whole-median nerve measurements in CTS and normal groups. FA values in CTS patients were significantly lower ($P < 0.001$) than normal subjects.

age-matched control group and CTS patients. The Mann-Whitney U-test was also used to compare groups based on the severity of CTS, gender, and in normal subjects, dominant/non-dominant wrists. The Wilcoxon test was used to compare FA and ADC measurements within the normal group. The Pearson's correlation test was used to relate age to DTI measurements in normal subjects and to relate DTI and nerve conduction measurements in all subjects. A $P < 0.05$ was considered significant for all tests.

When the Student's t-test revealed a significant difference in FA and ADC between CTS and control subjects, an additional receiver operating characteristics (ROC) analysis was performed to determine the area under the ROC curve (AUC). The AUC provides a value between 0.5 and 1.0 that is related to the diagnostic accuracy of a test, and it can distinguish between CTS and control subjects. The cut-off value reported is the value that achieved maximum sensitivity and specificity within a 95% confidence interval (CI).

Results

Normal subjects

The mean FA and ADC were 0.712±0.047 and 1.005±0.119×10^{-3} mm2/s in females, and 0.673±0.036 and 1.008±0.105×10^{-3} mm^2/s in males, respectively. The differences between genders were not statistically significant.

The examined wrist was dominant for 12 of the 30 control subjects. In the dominant wrists, mean FA for the median nerve was 0.695±0.528 and ADC was 0.700±0.447×10^{-3} mm^2/s. No statistically significant differences were found between dominant and non-dominant wrists.

In control subjects, mean FA of the focal carpal tunnel measurement was 0.599±0.063, and the mean ADC was 1.046±0.271×10^{-3} mm^2/s. For the whole nerve measurement, the mean FA was 0.698±0.047, and the mean ADC was 1.033±0.118×10^{-3} mm^2/s. There was no statistically significant difference between the ADC measurements of the nerve at the carpal tunnel level and the whole nerve; however, the mean FA was significantly lower at the carpal tunnel level ($P < 0.001$).

Age was significantly and positively correlated with ADC ($P < 0.05$, $\rho=0.442$) and negatively correlated with FA ($P < 0.01$, $\rho=0.549$).

CTS patients

The mean FA and ADC values and their standard deviations are summarized in Table 1 for primary normal controls, age-matched controls, and CTS patients. CTS patients showed significantly lower FA values in both the whole nerve and focal carpal tunnel measurements compared to both the primary and age-matched control group ($P < 0.001$). No significant differences were observed between ADC measurements. A mild overlap between FA values in focal and whole-nerve measurements was found (Fig. 4).

Table 1. FA and ADC values (mean±standard deviation) in CTS and normal groups

	Carpal tunnel level		Whole media nerve	
	FA[a]	ADC (×10^{-3} mm^2/s)	FA[b]	ADC (×10^{-3} mm^2/s)
CTS (n=57)	0.475±0.078	1.129±0.228	0.589±0.078	1.064±0.136
Normal (n=30)	0.599±0.063	1.046±0.271	0.698±0.047	1.033±0.118
Age-matched normal (n=12)	0.596±0.076	1.077±0.262	0.667±0.040	1.080±0.090

No significant difference was observed between the ADC measurements of normal, age-matched normal, and CTS groups.
[a,b]$P < 0.001$ for CTS vs. normal group and CTS vs. age-matched normal group.
FA, fractional anisotropy; ADC, apparent diffusion coefficient; CTS, carpal tunnel syndrome.

Table 2. FA and ADC values (mean±standard deviation) in normal subjects, mild CTS patients, and severe CTS patients

	Carpal tunnel level		Whole media nerve	
	FA[a]	ADC (×10^{-3} mm^2/s)	FA[b,c]	ADC (×10^{-3} mm^2/s)
Normal (n=30)	0.599±0.063	1.046±0.271	0.698±0.047	1.033±0.118
Mild CTS (n=18)	0.501±0.059	1.029±0.215	0.623±0.076	1.034±0.148
Severe CTS (n=39)	0.462±0.084	1.175±0.222	0.573±0.075	1.078±0.129

[a]$P < 0.001$ for normal vs. mild CTS.
[b]$P < 0.01$ for normal vs. mild CTS.
[c]$P < 0.05$ for mild vs. severe CTS.
FA, fractional anisotropy; ADC, apparent diffusion coefficient; CTS, carpal tunnel syndrome.

Of the 57 CTS wrists, 18 were classified as "mild CTS", and 39 were "severe CTS". Compared to mild CTS patients, severe CTS patients had lower FA values in both the whole median nerve and focal carpal tunnel measurements (Table 2), but only the whole-nerve difference was statistically significant ($P < 0.05$). Moreover, the focal carpal tunnel FA and both ADC measurements were not significantly different between mild and severe CTS nor was there a significant correlation between FA, ADC, sensorial-nerve conduction velocity, and motor-distal latency values. Mild CTS patients had significantly less focal and whole-nerve FA compared to the primary control group (Table 2).

The results of the ROC analysis are summarized in Table 3, and the ROC curves for both the focal carpal tunnel and whole-nerve FA are shown in Fig. 5. The AUC was 0.905 (95%CI, 0.842–0.969) in focal carpal tunnel measurements and 0.884 (0.815–0.953) in whole-nerve measurements. A cut-off value of 0.554 in focal carpal tunnel FA values showed a maximum sensitivity of 80.7% and a maximum specificity of 80%, whereas 0.660 in whole-nerve FA showed a maximum sensitivity of 82.5% and a maximum specificity of 80%.

Discussion

CTS is the most common entrapment neuropathy that affects the median nerve at the level of the carpal tunnel. Clinically, patients present with a dull aching discomfort in the hand, paresthesia in the median nerve distribution and, in advanced cases, thenar atrophy. Although electrodiagnostic techniques are considered the single-most accurate diagnostic test, their false negative and false positive rates have been well documented. Together, nerve conduction studies and electromyography can confirm a CTS diagnosis with 85% sensitivity and 95% specificity; however, the combined use of electrodiagnostic findings and symptom characteristics provides the most accurate diagnosis (3, 13). This accuracy is not optimal; therefore, more accurate diagnostic techniques are needed.

DTI is used mostly to visualize white matter fiber tracts in the central nervous system (4). Peripheral nerve DTI was first applied to the sciatic nerve by Skorpil et al. (5) and then to the peripheral nerves by Hiltunen at al. (7). Andreisek et al. (14) showed precision in the quantitative evaluation of the median nerve through DTI. The most studied peripheral nerve with DTI is the median nerve because of the potential application to CTS (8, 11, 12). In these studies, a decreased FA was the most commonly observed finding, which is consistent with our results (8, 11, 12), and one study has shown different FA changes in CTS compared to control subjects (12); healthy subjects show an increase in

Table 3. ROC analysis results

	Carpal tunnel level	Whole media nerve
Cut-off FA value	0.554	0.660
Area under curve (95% confidence interval)	0.905 (0.842–0.969)	0.884 (0.815–0.953)
Sensitivity	80.7%	82.5%
Specificity	80%	80%

FA, fractional anisotropy; ROC, receiver operating characteristics.

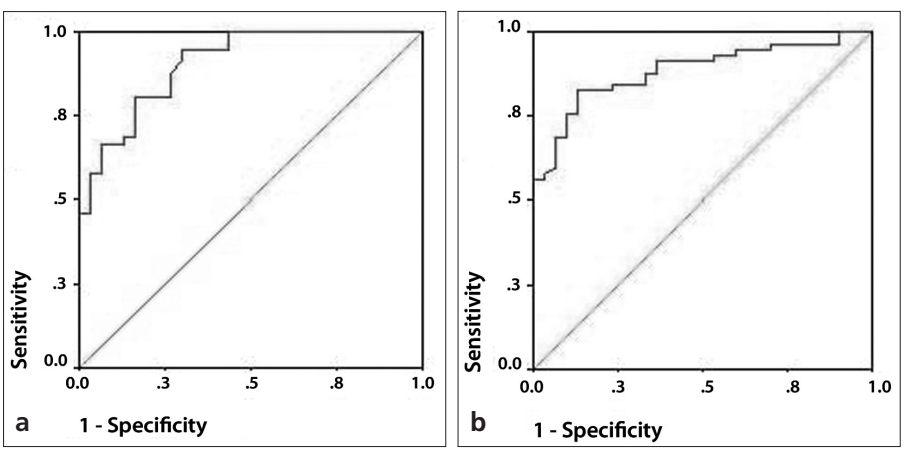

Figure 5. a, b. ROC curves for focal carpal tunnel **(a)** fractional anisotropy (FA) measurements (AUC=0.905) and whole median nerve **(b)** measurements (AUC=0.884).

FA and radial diffusivity and a decrease in ADC along the median nerve at the carpal tunnel, whereas CTS patients showed the opposite. In our control group, we observed lower FA values in carpal tunnel compared to whole-nerve measurements. ADCs of the median nerve demonstrated no significant differences between carpal tunnel whole-nerve measurements, which is also consistent with a previous study (8). Because peripheral nerve DTI is a new method, sequence parameters and measurement techniques may differ between studies and cause these discrepancies.

In our study, we observed a significant positive correlation between age and ADC and a negative correlation between age and FA. These findings are consistent with a previous DTI study of the median nerve (8) and reports on age-related brain changes (15). However, the correlations between age and DTI measurements are mild. A decrease in the number of myelinated nerve fibers with advancing age (16) could cause a decrease in FA and an increase in ADC. We observed no FA or ADC difference between dominant and non-dominant wrists.

The main result of this study is a statistically significant FA decrease in CTS patients compared to both control and age-matched control subjects. In addition, ROC analysis found an AUC of 0.905 in focal carpal tunnel measurements and 0.884 in whole median nerve measurements. These results indicate that FA measurements at the carpal tunnel level exhibit a higher true-positive rate than whole-nerve FA measurements. No significant difference between CTS and normal subjects' ADC measurements was observed.

ADC measures the degree to which water molecules are restricted in their overall movement, and FA measures the degree to which their movement is restricted in a particular direction. In peripheral nerves, anisotropic diffusion is prominent because water diffusion is restricted in certain directions by axonal tubules and the nerve's myelin sheath (17). CTS may be described pathophysiologically as chronic nerve compression where the initial change is a breakdown in the blood-nerve barrier followed by subsequent sub-perineurial and endoneurial edema, perineurial and epineurial fibrosis, demyelination (first localized, then diffuse), and Wallerian degeneration (18), all of which can affect water diffusion in the nerve fiber. In our study, we observed FA decrease in CTS patients but comparable ADC values in CTS and normal patients. In an animal study (19), Wallerian degeneration in the peripheral nerves has been shown to cause decreased anisotropy in tie-injured and degenerated nerve fibers but normal ADC. Pierapoli et al. (20) further showed that Wallerian degeneration in the central nervous system causes severely reduced anisotropy but slightly increased ADC. In CTS, Wallerian degeneration and epineurial and perineurial fibrosis co-occur; therefore, it is not surprising to find reduced FA and comparable ADC values in CTS patients compared to normal subjects. Moreover, such a finding is consistent with a study by Khalil et al. (11).

Using ROC analysis, we determined cut-off values for diagnosing CTS with focal carpal tunnel and whole-nerve FA values, which can be used clinically. This cut-off was 0.660 for the whole median nerve measurement, which yielded 82.4% sensitivity and 80% specificity. The focal carpal tunnel cut-off was 0.554, which yielded 80.7% sensitivity and 80% specificity.

Evaluation of DTI measures according to CTS severity demonstrated a mild FA decrease in severe CTS patients, which was accompanied by a significant whole-median nerve measurement difference. The difference between focal carpal tunnel measurements was not significant. While this finding seems to conflict with the higher AUC of focal carpal tunnel FA measurements, the use of multiple centers for completing electrodiagnostic testing may cause this lack of correlation.

Whole median nerve FA values are particularly important in CTS because in some situations determining the exact compression level at the carpal tunnel level is difficult. Therefore, focal measurements at the carpal tunnel may demonstrate variability, but a whole-nerve evaluation is still helpful for diagnosing CTS.

We could not make intrasubject comparisons because of the high number of patients with bilateral CTS, which is a limitation of this study but not unusual. Bilateral involvement of CTS is common and often prevents the use of the contralateral wrist as an internal control.

In conclusion, although there is some overlap between CTS and control subjects with respect to DTI measurements, the FA value may provide helpful diagnostic information. However, sensitivity and specificity levels were not high enough to be used as a single criterion of CTS.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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