

*Research Article***Carpal tunnel syndrome in rheumatoid arthritis patients: evaluation of the depth by ultrasonography****Elsaman AM***, **Hamed A****, **Borai A***** and **Radwan AR***

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Abstract

Ultrasound (US) is one of the most widely used tools for diagnosis and evaluation of carpal tunnel syndrome (CTS). US achievement is comparable to the gold standard electrophysiological studies. Depth of the carpal tunnel is a promising, relatively new sonographic parameter used for assessment of the median nerve. Previously it was evaluated in cadavers, normal individuals and in idiopathic carpal tunnel. The objective of this work is to address the value of the depth of the carpal tunnel (DCT) in patients with Carpal tunnel syndrome (CTS) and Rheumatoid arthritis (RA) by comparing it to healthy volunteers using US. Electrophysiology was used as a gold standard and other US parameters like cross sectional area (CSA) and flattening ratio (FR) were considered. The study was conducted in 112 non-diabetic RA patients having carpal tunnel syndrome (unilateral n=60, bilateral n=52) evidenced by electrophysiological diagnosis according to the criteria of the American Association of Electrodiagnostic Medicine. Furthermore, 40 hands from 20 healthy volunteers were examined. The mean age of the patients was 59.1±8.08 years. The female to male ratio was 96:17 in CTS patients. The difference between patients and healthy controls was significant in all three parameters and was highest at the DCT, followed by CSA and then FR. We can conclude that DCT increased obviously in RA patients with CTS, and this augmentation was related to tenosynovitis more than synovitis.

Keywords: Rheumatoid arthritis; carpal tunnel syndrome; electrophysiology; ultrasonography; depth of the carpal tunnel

Introduction

Rheumatoid arthritis (RA) is a chronic polyarticular inflammatory disease, affects mainly small joints of the hand and foot. It has a prevalence of approximately 1% of the worldwide population. RA is commonly associated with peripheral vasculopathy and entrapment neuropathy causing distal sensory, and combined sensory and sensorimotor neuropathy⁽¹⁾.

Carpal tunnel syndrome (CTS) refers to the compression of the median nerve at the

carpal tunnel and can result in sensory and motor disturbances in areas of the hand supplied by this nerve, leading to pain and loss of function⁽¹⁾. CTS is the commonest entrapment neuropathy associated with RA.

This is believed to be a result of compression of a peripheral nerve by tenosynovitis and synovitis in a closed space⁽²⁾. CTS affects 4 to 10% of rheumatoid arthritis patients with variable prevalence depending on ethnicity, disease duration and method of CTS diagnosis⁽³⁻⁵⁾.

Synovitis, tenosynovitis and tendonopathy are basic features found frequently in RA patients especially in the flexors of the wrist⁽⁶⁾. Clinical evaluation of CTS in RA patients is usually not reliable, because painful hand in RA patients interfere with CTS manifestations, although electrophysiological evaluation is considered gold standard for CTS diagnosis, it is counted by many patients an invasive maneuver and

they refuse it⁽⁴⁾. US is a practical, painless, rapid and bedside test preferred by most of the patients⁽⁴⁾.

Evaluation of the depth of the carpal tunnel has been inadequately addressed in the literature on CTS especially those with RA, as most previous studies evaluated the depth of the carpal tunnel in normal individuals and not in CTS patients^(4,17).

In our study we tried to measure the depth of carpal tunnel (DCT) in RA patients with CTS and correlate it to the other sonographic parameters in electrophysiologically confirmed CTS patients.

Patients and Methods

All participants enrolled in our study were informed about the methodology and aims of the study, and a written informed consent was obtained. The study protocol was accepted by the local ethics committee of Sohag Faculty of Medicine, Egypt. Personal and medical information were kept confidential and were not made available to another party.

RA patients with clinical suspicion of CTS based on the presence of two or more of the primary criteria of the American Academy of Neurology, were recruited from the outpatient clinics of Neurology and Rheumatology of Sohag University Hospitals⁽¹⁷⁾. They all were first directed to the Neurologist for conducting clinical and neurophysiological examinations, and then to the Rheumatologist for ultrasonographic examination. The rheumatologist was blinded to the patients' diagnosis and the neurologist was also blinded about sonographic examination results.

A descriptive cross-sectional study was performed on the hands of 123 patients aged 20 years or above, all of them were classified as RA patients according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria⁽¹⁸⁾; with unilateral (n=80) or bilateral (n=43) CTS, giving a total of 123 affected hands. The study also included 40 hands from 20 healthy volunteers of the same age group and comparable male to female ratio.

Patients with any other known cause of CTS like acromegaly, hypothyroidism, amyloidosis, pregnancy and diabetes mellitus were excluded from the study.

Ultrasonographic and electrodiagnostic measurements were done to all patients and healthy volunteers.

American Association of Electrodiagnostic Medicine (AAEM) criteria were considered as gold standard for CTS diagnosis^(19,20). The electrophysiological evidence of slowing of distal median nerve conduction includes prolongation of distal sensory and/or motor latency of median SNAP and/or CMAP \pm reduced SNAP/CMAP amplitude of the median nerve⁽¹⁹⁾.

Regarding motor nerve conduction, compound muscle action potential (CMAP) both were recorded by (Ag/AgCl) electrodes (Nihon Kohden Co, Japan) positioned over the motor points of abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles for median and ulnar nerve studies. The median nerve was stimulated at a distance of 4 cm from the active electrode, between the tendons of the flexor carpi radialis and palmaris longus muscles at the wrist and at the elbow. The ulnar nerve was stimulated at the wrist at a remoteness of 4 cm from the recording electrode and at the elbow. Distal motor latency, conduction velocity, and CMAP amplitude were estimated.

Regarding sensory nerve conduction, sensory conduction velocity, sensory nerve action potential (SNAP) amplitudes, and distal sensory latency were assessed by antidromically stimulated median and ulnar nerves using ring electrodes from the second, fourth, and fifth digits for the median nerve and ulnar nerves. Both nerves were stimulated at the wrist 12 cm from the active electrodes. A minimum room temperature of 20°C and extremity distal skin temperature of >22°C were considered for all electrophysiological studies. C5, L4 and T1 radiculopathy were excluded by extensor indices, thenar, and hypothenar electromyography.

Distal motor latency > 4 ms, distal sensory peak latency of > 3.0 ms, sensory

conduction velocity < 40 m/s and sensory latency difference of > 5 ms between median and ulnar SNAPs in the fourth finger were taken as cutoff points for diagnosis of CTS according to our unit values⁽¹⁴⁾. All electrodiagnostic examinations were done by the same examiner.

Ultrasonographic testing was performed using a 7-12 MHz (General electric logic E, China) linear probe. They were done in the sitting position, with the elbow flexion and the wrist directed upward. The median nerve was recognized by being the most superficial fascicular structure in the carpal tunnel under the flexor retinaculum, with hyperechoic sheath⁽¹⁵⁾. DCT, CSA and FR were measured in all participants. Longitudinal and transverse scans were done of the median nerve at the canal outlet (which was considered as the distal edge of the flexor retinaculum for DCT measurement)⁽¹⁶⁾, and at the canal inlet (proximal margin of the flexor retinaculum) for CSA and FR⁽¹⁷⁾.

Capsule reflection over the Capitate bone at the canal outlet was used as a land mark for DCT measurement⁽¹⁸⁾ (fig. 1). By tracing the nerve distally in the transverse scan, the flexor retinaculum and the capitate capsule appear together at one single point. The measurement was taken at that point and then longitudinal measurement was calculated. Mani et al., and Elsaman et al., used the same level for measuring the DCT^(19, 20).

Cross sectional area was measured by tracing the nerve surface in axial section and the hyperechoic epineural rim was omitted⁽²¹⁾. FR was calculated in transverse section by dividing the maximum length to the maximum width of the median nerve⁽²²⁾. CSA and FR were measured twice and if there was difference, the mean of the two measurements was considered. DCT measurement was considered when it was the same in axial and sagittal planes. A difference up to 2 mm was accepted. CSA more than 1 cm² and FR more than 2.5 were considered as CTS⁽²³⁾.

To avoid faulty calculation of the median nerve the probe was just touching the skin without any pressure⁽²⁴⁾. A perpendicular

angle of the probe was conserved in all examinations⁽²⁵⁾.

Tenosyovitis of carpal tunnel tendons for RA patients was also evaluated using semiquantitative score⁽²⁶⁾. Tenosynovitis was binary evaluated (0/1) for B mode and Power Doppler (PD). Grade 0 was considered as no abnormal hypo/anechoic material in the sheath/no abnormal Doppler signal inside/around it. B mode grade 1 was defined as hypo/anechoic area in the tendon sheath. PD grade 1 was defined as Doppler signal in the tendon sheath or inside the tendon. Grades from all joints and tendons US evaluations were noted on a worksheet. Tendons were examined in sagittal and axial view. Wrist joint was assessed from the palmar side for synovitis by B mode and PD. The same binary score was used for evaluation of the wrist joint on the palmar side by using axial and sagittal scans⁽²⁷⁾ (fig. 2 and 3). Synovitis was graded by binary score grade 1 synovitis and grade 0 no synovitis on B mode and PD (grade 0 or 1) according to the presence or absence of PD signals⁽²⁸⁾.

Data were presented as arithmetic mean \pm SD, and median (range) according to normality tested with the Kolmogorov-Smirnov test. Student's t-test and the Mann-Whitney test were used for normally and non-normally distributed variables; respectively. Comparisons of percentages of qualitative data were tested using the Pearson's Chi square test or Fisher's exact test. The correlation between two quantitative data was done using Pearson's or Spearman's Correlation test. Sensitivity and specificity of US measurements in CTS patients were calculated taking electrophysiology as the gold standard for CTS diagnosis. Statistical Package for the Social Sciences (SPSS) software (version 24.0, SPSS Inc., Chicago, IL, USA, May 2016) was used in all statistical analyses. A p value < 0.05 was considered significant. Microsoft Excel 2016 software was used to generate charts from data obtained from SPSS output.

In the patients group, motor latency, CMAP, motor conduction velocity (MCV), Peak latency, SNAP and sensory

conduction velocity (SCV) were not normally distributed and medians and range were considered for them, while age and sonographic measures were normally distributed and hence the mean and standard deviation were considered for them.

Results

The mean age of the patients with CTS was 52 ± 12.0 years and the mean age for healthy controls was 39.1 ± 8.08 years. Seventy eight percent of patients were female and 70% of the healthy volunteers were female. So, both groups were age and sex matched with non-significant differences (table 1).

Electrophysiology:

For the CTS patients group, the motor latency median was 0.9 (range, 3.8-9.6) milisecond, CMAP median was 4.81 (range 1.3-16.1) mV, and median MCV 39.4 (range, 31.3-112.4) m/sec. There were nine patients with Martin Gruber anastomosis in whom there were spuriously fast median conduction velocities. The peak latency median was 4.81 (range, 2.0-8.1) millisecond, median SNAP was 11.14 (range, 1.2-26.12) uV, and the median SCV was 40.1 (range, 24.3-70.2) m/sec.

For the control group, the motor latency median was 2.7 (range, 2-2.8) milisecond, the mean CMAP was 7.3 ± 1.52 mV, median MCV was 46.2 (range, 38-08) m/sec, mean peak latency was 2.48 ± 0.46 milisecond, median SNAP was 24.70 (range 18-27.4) uV and the mean SCV was 40.41 ± 0.90 m/sec.

The motor latency, peak latency and SNAP differences between the two groups were highly significant with a p value of < 0.0001 . The MCV and SCV differences were significant ($p = 0.019$ and 0.028 ; respectively). The CMAP difference was non-significant ($p = 0.061$).

Our study revealed that there is a significant correlation between the severity of tenosynovitis and neurophysiological parameters of the median nerve (motor distal latency > CV > CMAP).

Ultrasonography:

The mean CSA for the CTS patients was 1.02 ± 0.38 cm², and for the healthy volunteers it was 0.89 ± 0.08 cm². There was a significant difference in the CSA at the canal inlet between the CTS patient and healthy control groups (p value < 0.0001).

Regarding FR, the mean value in the patients was 2.12 ± 0.69 and in the healthy volunteers the mean was 2.48 ± 0.34 , the difference being significant ($p, < 0.0001$).

Mean DCT mean in the patient group was 1.19 ± 0.31 cm and in the healthy controls it was 0.83 ± 0.12 cm, the difference between the two groups being significant ($p < 0.0001$).

Synovitis was detected (by B mode and/or PD) in 87 RA cases (70.7%) compared to 6 controls (30%); with a significant difference ($p < 0.0001$). Tenosynovitis was found in 22 RA cases (42.2%) compared to zero among controls, also with a significant difference ($p < 0.0001$).

A positive and significant relation was found between and tenosynovitis and US measures of the median nerve, being most evident with DCT ($p < 0.0001$) followed by CSA ($p =$), but not with FR. Table 1. Summarizes sonographic and electrophysiologic results. Using the Spearman Correlation test to study the concordance between US results and disease duration among RA patients, we found that FR was the most item correlated with duration ($r = 0.041$, $p = 0.012$), followed by DCT ($r = 0.318$, $p = 0.098$) and lastly CSA ($r = 0.122$, $p = 0.387$). The correlations between disease duration and each of DCT and CSA were non-significant.

Furthermore, Spearman correlation test was used to study the concordance between electrophysiologic and sonographic results of our patients. The results of this statistic revealed, that motor latency and peak latency showed positive, strong and highly significant correlations with all of the three US measures, while MCV showed positive, moderate and significant correlations. On the other hand, SNAP showed negative,

moderate, significant to highly significant correlations with US measures, while SCV showed negative, weak and significant correlations. Lastly, CMAP and onset

latency showed non-significant correlations with any of the US findings. Table 2 summarizes the results of these correlations.

Table (1): Comparison between patients and controls regarding ultrasonographic and electrophysiologic measurements

| Measure | Patients# | Controls# | P value |
|---|-------------------|----------------|---------|
| Personal data | | | |
| Age (years) | 42±12.0 | 39.1±8.08 | 0.190 |
| Sex (male:female) | 27:96 | 0:10 | 0.762 |
| Electrophysiologic data | | | |
| Motor latency (msec) | 0.9(3.8-9.7)^ | 2.7(2-2.8)^ | <0.0001 |
| CMAP (mV) | 4.81(1.3-17.1)^ | 7.3±1.42 | 0.61 |
| MCV (m/sec) | 39.4(31.3-112.4)^ | 47.2(38-08)^ | 0.19 |
| Peak latency (msec) | 4.81(2.0-8.1)^ | 2.48±0.47 | <0.0001 |
| SNAP (uV) | 11.14(1.2-27.12)^ | 24.70(18-27.4) | <0.0001 |
| SCV (m/sec) | 40.1(24.3-70.2)^ | 0.41±0.90 | 0.28 |
| Ultrasonographic data | | | |
| Cross sectional area (CSA) (cm ²) | 1.02±0.38 | 0.89±0.08 | <0.0001 |
| Flattening ratio (FR) | 3.12±0.79 | 2.48±0.34 | <0.0001 |
| Depth of the carpal tunnel (DCT) (cm) | 1.02±0.19 | 0.79±0.1 | <0.0001 |

^ median and range was used instead of mean ± SD (for non normally distributed data), # test was done for 111 hands from 123 RA patients and 40 hands from 20 controls.

Table (2): Spearman Correlation tests between ultrasonographic and electrophysiologic measurements among patients:

| | Circumference | | Flattening ratio | | Depth | |
|---------------|---------------|---------|------------------|---------|-------|---------|
| | r | P | r | p | R | p |
| Motor latency | 0.819 | <0.0001 | 0.733 | <0.0001 | 0.712 | <0.0001 |
| CMAP Amp | -0.116 | 0.306 | -0.134 | 0.237 | - | 0.330 |
| MCV | 0.478 | 0.040 | 0.063 | 0.009 | 0.412 | 0.038 |
| Onset latency | -0.003 | 0.983 | -0.129 | 0.429 | 0.116 | 0.476 |
| Peak latency | 0.804 | <0.0001 | 0.706 | <0.0001 | 0.810 | <0.0001 |
| SNAP Amp | -0.713 | <0.0001 | -0.478 | 0.006 | - | 0.002 |
| SCV | -0.312 | 0.046 | -0.327 | 0.033 | 0.089 | 0.029 |
| | | | | | 0.402 | |

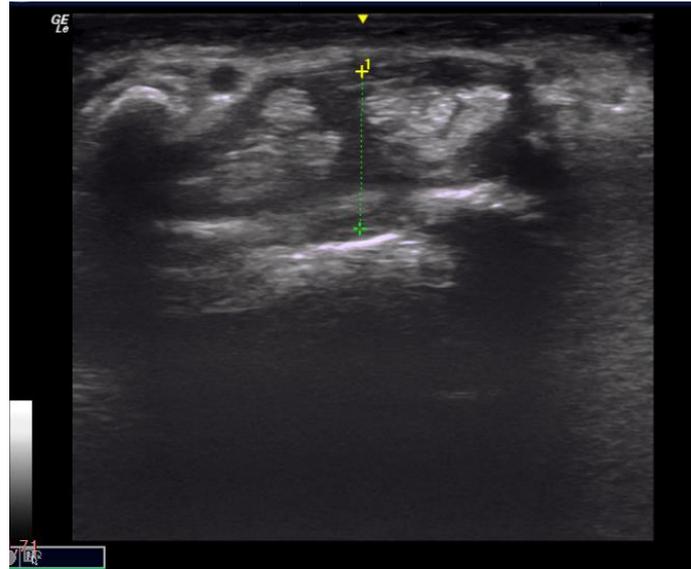


Figure 1. Wrist, axial at the level of the canal outlet showing depth of the carpal tunnel at the capitate level and median nerve, flexor retinaculum and flexor tendons.

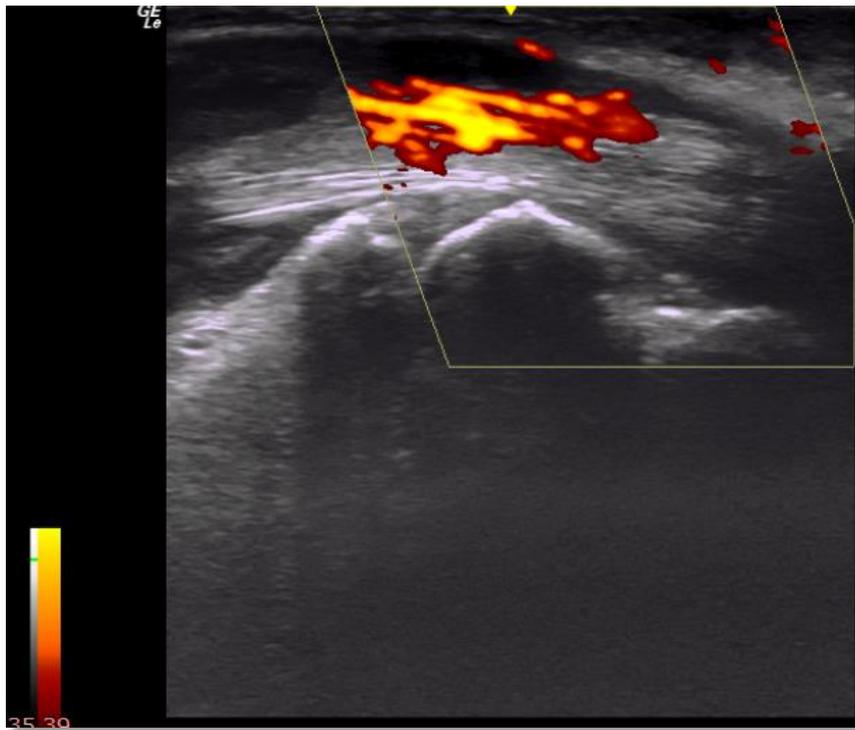


Figure 2. Wrist, palmar midline sagittal, showing flexor digitorum superficialis power Doppler activity over the distal end of the radius, lunate and capitate in active rheumatoid arthritis patient.

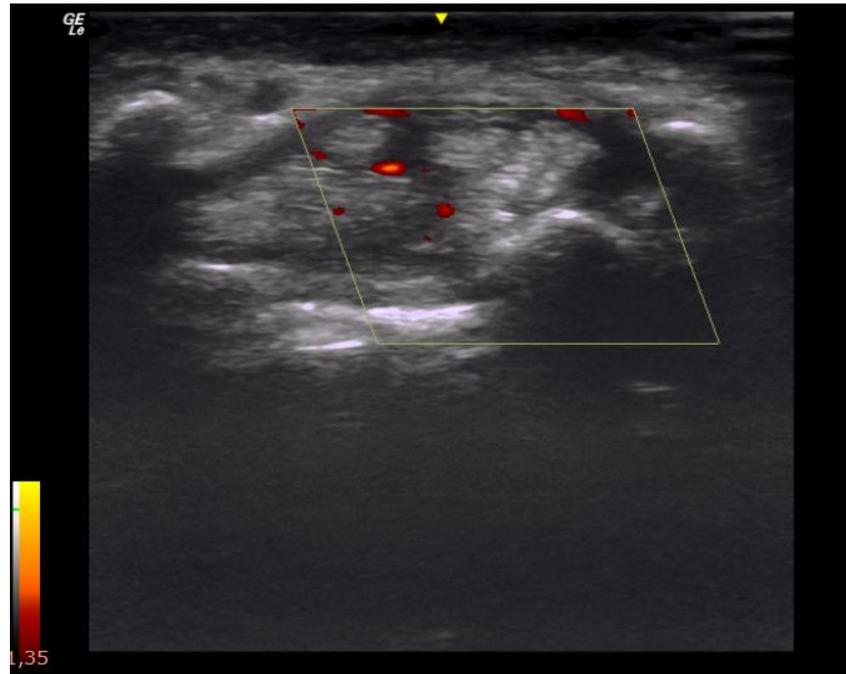


Figure 3. Wrist, palmar axial, showing power Doppler activity of the flexor tendons between pisiform and scaphoid bones with underlying carpal bones and flexor retinaculum roof.

Discussion

The gold standard for CTS diagnosis is usually the electrophysiological examination. It has some advantages in early diagnosis and in mild cases, but in some severe cases and severe peripheral polyneuropathy it shows no response. Besides, it is a painful invasive technique and it has limited ability to detect a bifid median nerve⁽²⁴⁾.

Ultrasonography increasingly becoming a basic and practical imaging method for the diagnosis of CTS. It is a painless and noninvasive technique, which gives a direct view of the carpal tunnel and the cause of the nerve compression and it is furthermore, able to detect congenital anomalies of the median nerve. Nevertheless, US examination is dependent on the operator and needs training of the examiners before conducting a study⁽²⁵⁾.

In our study, DCT were estimated at the canal outlet and CSA and FR at the inlet. At the canal outlet the capitate bone has a distinctive capsule reflection which was used as a landmark. For CSA and FR also measurement at the inlet is agreed in many

literatures^(22, 23). Ethnicity, age and body mass index play a major role in changing the sensitivity of each level^(25, 27-28).

Most of the previous ultrasonographic parameters were concerned with measuring the nerve itself, but DCT is a real evaluation of the canal dimension. The results of our study showed that depth increases in most of the cases with RA and CTS in comparison to healthy volunteers. This parameter has a comparable sensitivity and specificity in relation to CSA and FR. The difference between diseased patients and healthy controls was highest at the DCT followed by CSA and finally FR. In a study done on cadavers⁽³⁾, the depth of the carpal tunnel was found 0.83 ± 0.09 cm whereas the DCT in our study was measured 1.02 ± 0.19 cm in CTS patients and 0.99 ± 0.1 cm in the healthy control group. The small difference between the two studies may be explained by the difference in ethnicity between the two groups and also by using cadavers in the study⁽³⁾. Another study found DCT mean was 1.02 ± 0.19 cm which is lower than our results. This study measured the depth in idiopathic CTS. This could clarify the effect

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of synovitis and tenosynovitis on the DCT⁽¹⁷⁾.

We also found a relation between tenosynovitis and both US and electrodiagnostic parameters more than that we found between synovitis and the same parameters, this can be attributed to the fact that the median nerve in the carpal tunnel lies immediately superficial to the flexor tendons, while the joint space located deeper to those tendons. This was widely different from the results obtained by Karadag et al, which found that there is no relation between disease activity or wrist activity and CTS. In their study they had patients with very long disease duration in comparison to ours (96.7±8.3), they also included diabetic patients. Furthermore; they did not use DCT parameter nor FR in their US parameters. Additionally, most of their patients either had no or mild wrist activity⁽¹⁸⁾.

A well-known shortcoming of using electrodiagnostic measures as a gold standard reference is, their high false negative rate of up to 20%, which would raise the false positive value of sonographic measures when using electrodiagnostic measures as a gold standard (36). To avoid this high ratio of false negatives, we used the AAEM criteria, which included both clinical and electrophysiological evidence of CTS⁽¹⁷⁾.

In conclusion, DCT is a new promising method for the detection of CTS. Tenosynovitis plays a crucial role in initiating CTS in RA patients. Much more work is needed to evaluate this parameter in different types of CTS.

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