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ORIGINAL ARTICLE

Comparison of the median and ulnar nerves of rheumatoid arthritis patients and healthy subjects by ultrasound

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ABSTRACT

Objectives: In this study, we aimed to investigate ulnar and median nerve cross-sectional areas (CSAs) by ultrasonography in RA patients who had no signs or symptoms of neurologic involvement.

Patients and methods: This case-control study was conducted with 76 participants (72 females, 4 males; mean age: 53.2+10.9 years; range, 18 to 65 years) between April 2011 and April 2013. Of the participants, 38 were RA patients without any signs or symptoms of ulnar or median nerve involvement, and 38 were healthy subjects. All participants were evaluated with ultrasound. The median and ulnar nerve CSAs were measured at the proximal inlet of the carpal tunnel using the pisiform bone as a landmark.

Results: There were no statistically significant differences between patients and controls in terms of median and ulnar CSAs ($p>0.05$). There were no correlations between median and ulnar CSAs of the dominant hand and age, height, weight, and disease duration. The median nerve CSA was >10 mm^2 in 24% of the RA patients and 14% of controls, but the difference was not statistically significant ($p=0.20$).

Conclusion: Similar median and ulnar CSAs were detected in RA patients and healthy controls. These findings cannot rule out a subclinical neurologic involvement.

Keywords: Median nerve, rheumatoid arthritis, ulnar nerve, ultrasonography.

Peripheral neuropathies, including both compressive and noncompressive neuropathies, are the most common neurologic manifestations of rheumatoid arthritis (RA).[1] Entrapment neuropathies are diagnosed in approximately 45% of RA patients.[2] In a retrospective cohort study on 1,070 patients with RA, the incidence of carpal tunnel syndrome (CTS) was reported to be 6.8%, although CTS did not correlate with disease activity or duration of RA.[3] Recent studies indicate a pooled prevalence of 5.5% for CTS in RA, which is not strikingly different from that of the general population ranging from 2.7 to 5.8%.[4]

Recently, musculoskeletal ultrasound (US) came into use for the detection of nerve entrapment syndromes.[5] It presents a cost-effective imaging modality for peripheral nerves with high-frequency transducers enabling the identification of traumatic, neoplastic, and compressive pathologies.[6] Ultrasonography may detect CTS, subclinical CTS, and other abnormalities with sensitivities and specificities ranging from 65 to 97% and 73 to 98%, respectively.[7,8] Therefore, some studies recommend an ultrasonographic examination in patients with RA.[9,10] Subclinical neuropathy can

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exist in 65 to 85% of patients with RA, depending on the method of examination.[11] Subclinical CTS has a pooled prevalence of 14% in patients with RA whereas that of the general population is between 7 and 16%.[4,12]

In a study investigating the incidence of upper extremity nerve compression in RA patients using high-frequency US, the nerve compression rate was significantly higher than healthy controls (15.0% *vs.* 3.3%, p=0.046).[10] Several sonographic studies reported CTS to be more common in RA patients than in healthy controls.[13] However, studies regarding subclinical nerve involvement present conflicting results. Therefore, in the current study, we aimed to compare the median nerve cross-sectional area (CSA) and the ulnar nerve CSA of RA patients with no signs or symptoms of neuropathy with those of the healthy controls.

PATIENTS AND METHODS

This case-control study was conducted with 76 participants (72 females, 4 males; mean age: 53.2+10.9 years; range, 18 to 65 years) in the outpatient clinic of the Gazi University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Divison of Rheumatology between April 2011 and April 2013. Of the participants, 38 were RA patients (37 females, 1 male; mean age: 53.2±12.2 years) without signs or symptoms of ulnar and median nerve involvement, and 38 were healthy controls (35 females, 3 males; mean age: 53.1±9.5 years). Rheumatoid arthritis patients diagnosed according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria were included in the study.[14] The exclusion criteria were patients with a diagnosis of CTS, paresthesia in hands, a positive Tinel's or Phalen's tests, motor weakness or atrophy in abductor pollicis brevis or abductor digiti minimi, history of fracture or surgery of the wrist or hand, neurological disorders affecting hand functions, such as peripheral nerve lesions, stroke, and severe systemic diseases, such as diabetes mellitus and chronic liver disease.

The age, sex, dominant hand, height, weight, disease duration, and medications were recorded. Patients were questioned for signs of CTS. Motor and sensorial examinations, Tinel's test, and Phalen's test were performed. Participants were evaluated in a sitting position facing toward the physician with the forearm in supine and rest position. All participants were evaluated with US (General Electric Logiq P5 device, 8-12 MHz high frequency transducer; General Electric Company, Boston, MA, USA) using the B mode by a physician blinded to patients' characteristics. The US probe was held lightly not to apply excessive pressure and affect the anatomic structure of the nerves. The median and ulnar nerve CSAs were measured at the proximal inlet of the carpal tunnel using the pisiform as a bony landmark. The CSA was manually measured using the 'manual trace' program of the device, excluding the hyperechoic sheath (Figure 1). Each measurement was repeated three times, and the mean value was used in the analyses. The measurements of healthy controls and RA patients were compared.

Statistical analysis

The data were analyzed using the SPSS version 11.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as the mean, standard deviation, minimum, and maximum values. Data distribution was evaluated using the Kolmogorov-Smirnov test. Independent samples t-test was used for intergroup comparisons of numerical variables, while the chi-square test was used for comparing categorical variables between groups. The associations between u- and m-CSA

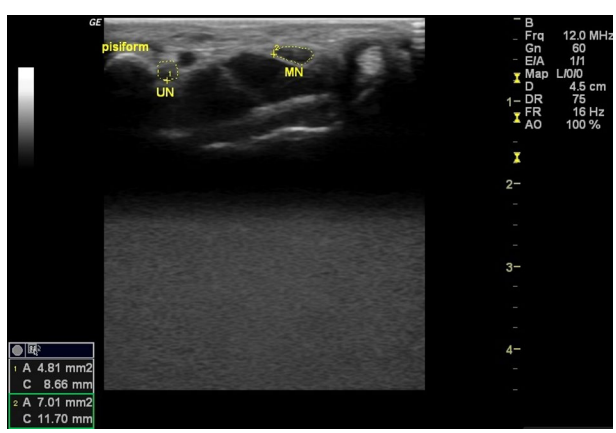

Figure 1. Transverse scan of the wrist demonstrating the median and ulnar nerves.

Table 1. Demographic characteristics of the participants

	RA patients (n=38)		Healthy controls (n=38)		
	n	Mean±SD	n	Mean±SD	*p*
Age (year)		53.2±12.3		53.1±9.5	0.97
Sex					0.30
Female	37		35		
Male	1		3		
Height (cm)		160.3±4.8		160.5±4.8	0.92
Weight (kg)		74.9±10.8		71.3±7.1	0.09

RA: Rheumatoid arthritis; SD: Standard deviation.

and age, height, weight, and disease duration were investigated using the Pearson correlation test. To achieve a difference of 2.8 mm^2 in the median nerve CSA between RA patients and controls with an alpha error of 0.05 and 80% power, 38 subjects were planned to be included in each group.[15] A *p* value of <0.05 was considered statistically significant.

Table 2. The mean CSA measurements of the ulnar and median nerves in RA patients and controls

	RA patients	Healthy controls	
	Mean±SD	Mean±SD	*p*
Right m-CSA (mm^2)	9.2±2.0	8.7±1.5	0.19
Left m-CSA (mm^2)	8.7±2.0	8.2±1.4	0.18
Right u-CSA (mm^2)	4.3±0.4	4.3±0.5	0.75
Left u-CSA (mm^2)	4.1±0.4	4.2±0.5	0.56

m-CSA: Median cross sectional area; RA: Rheumatoid arthritis; SD: Standard deviation; u-CSA: Ulnar cross sectional area.

Table 3. The correlation between the dominant hand ulnar nerve CSA values and clinical parameters in RA patients

	m-CSA		u-CSA	
	r	*p*	r	*p*
Age	0.07	0.66	0.01	0.97
Height	-0.02	0.90	-0.14	0.40
Weight	0.27	0.10	0.01	0.99
Disease duration	-0.06	0.71	-0.05	0.75

m-CSA: Median nerve cross-sectional area; RA: Rheumatoid arthritis; u-CSA: Ulnar nerve cross-sectional area; r: Pearson rho correlation coefficient.

RESULTS

The two groups did not differ in terms of age, sex, height, and weight (p>0.05 for all). Table 1 demonstrates the demographic characteristics of the study groups.

Of the RA patients, 65.8% (n=25) were on methotrexate treatment, 15.8% (n=6) on sulfasalazine, 15.8% (n=6) on leflunomide, 23.7% (n=9) on oral steroids, and 26.3% (n=10) on hydroxychloroquine. Of the patients, 34.2% (n=13) were on a combination therapy of disease modifying antirheumatic drugs.

When ulnar and median nerve CSAs were compared for right and left extremities between groups, no statistically significant difference was observed. Table 2 shows the mean CSA measurements of the two groups. No significant relationship was observed between the dominant hand median and ulnar nerve CSA values and age, height, weight, and disease duration in the RA group (p>0.05 for all; Table 3).

Of the RA patients, 24% had a median nerve CSA of >10 mm^2, whereas this rate was 14% in controls, with no significant difference between the groups (p=0.20). We detected bifid median nerve in a RA patient and excluded her data from the analyses.

DISCUSSION

We have found that there were no statistically significant differences in terms of ulnar and median nerve CSAs between patients with RA and healthy controls. In addition, CSA of the

dominant hand median nerve did not correlate with clinical parameters, including age, disease duration, and anthropometric measurements. Although the RA group had more patients with a median nerve CSA of >10 mm^2, the difference was not statistically significant. A cut-off point of 10 mm^2 has been suggested as the upper limit of normal CSA for the median nerve.[16]

It is known that wrist arthritis and tenosynovitis of the finger flexors may increase the risk of CTS during the course of RA. Anatomically, the transvers carpal ligament forms the roof of the carpal tunnel and the base of the Guyon canal. The increased pressure in the carpal tunnel may change its volume and thus affect the volume of the Guyon canal. Studies investigating the ulnar nerve by US are scarce. In a study on healthy individuals from the USA using US, the mean ulnar nerve CSA was reported to be 5.0 mm^2 in females.[17] Yalcin et al.[18] found a mean ulnar nerve CSA of 4.9±0.6 mm^2 at the Guyon canal and reported that this value could be used as a reference for the ultrasonographical diagnosis. In our study, the mean ulnar nerve CSA was within the proposed normal ranges (4.13 to 4.34 mm^2) and did not differ significantly between RA patients and healthy controls.

High-frequency US can evaluate the median nerve and the structures within the carpal tunnel. Ultrasound can display the alterations in the shape and echotexture of the entrapped nerve. The most common of these is flattening (notch sign), which results in decreased CSA at the compression site and swelling proximal to the compression point. In entrapment neuropathies, the echotexture of the nerve may be hypoechoic with an impaired fascicular pattern at the compression point and above.[19] Ultrasound is a relatively accessible, low-cost, noninvasive, and fast method[20,21] and has a sensitivity and specificity of 89% and 83%, respectively, for accurately detecting the median nerve CSA.[20] In a recent study investigating the frequency of CTS in RA patients, psoriatic arthritis patients, and healthy controls using electrophysiological and ultrasonographic findings, CTS was electrophysiologically detected in 13.2% of the RA patients, 15.4% of the psoriatic arthritis patients, and 3.5% of the healthy individuals. The threshold for the median nerve CSA was determined to be 10.5 mm^2 based on the receiver operating characteristics analysis, and the frequency of CTS was found to be 30% in the RA group according to this cut-off value.[22] In the present study, electrophysiological tests were not performed since the patients had no signs or symptoms of CTS.

In a study by Yağcı et al.,[23] 30 female RA patients and 30 healthy females without clinical and electrophysiological signs of CTS were enrolled to compare the median and ulnar CSAs. They detected a higher median nerve CSA at the radioulnar joint, pisiform, and hamatum levels. They also reported that if a median nerve CSA of 10 mm^2 at the pisiform level was considered a sonographic CTS criterion, 23 of 60 hands in RA patients and 5 of 60 hands in controls could be diagnosed with CTS. Therefore, they concluded that physicians should be careful not to over-diagnose RA patients as CTS by US. Similarly, Onat et al.[24] found higher values of CSA for the median, ulnar, and tibial nerves in RA patients compared to healthy controls.

Another study on 154 RA patients without signs or symptoms of neuropathy detected that 10% of the patients had a median nerve CSA of >10.0 mm^2, as commonly reported in patients with mild CTS.[25] Furthermore, they reported that the mean CSA of the median nerve (8.3±1.4 mm^2) in RA patients was similar to the controls, which is in line with our findings. Hammer et al.,[26] in their study comparing the median nerve CSA across CTS patients, RA patients, and healthy subjects, reported that the median nerve CSA was significantly higher in the CTS group, whereas it was comparable between RA patients and healthy controls. In addition, they found no significant correlations between the median nerve CSA and weight and height in the RA group. The findings of this study are also similar to our results.

In another study, authors did not find an association between the mean CSA and height, weight, age, or disease duration, which is in accordance with our findings. They remarked that these results suggest no change in the size of the nerves during ongoing inflammation. While they reported a CSA of >10 mm^2 in 10% of their cohort,[25] 24% of our RA patients had a median nerve CSA of >10 mm^2, though both these rates did not exhibit a statistically significant difference between RA patients and healthy controls.

In a recent study comparing median nerve stiffness by real-time tissue elastography (RTE) in patients with and without RA, no significant differences were observed between the groups in the median nerve CSA, which is similar to our results. However, they stated that the strain ratio of the median nerve was significantly higher in the RA group compared to healthy controls at the inlet of the carpal tunnel, suggesting RTE is highly sensitive in detecting median nerve degeneration. They concluded that RTE was sensitive in differentiating mild and moderate-to-severe CTS patients from healthy individuals.[27]

The inclusion of a control group, blinded design, and evaluation of the ulnar nerve in addition to the median nerve are the strong elements of this study. The main limitation of the present study is the lack of an inter- and intrarater reliability assessment. Another drawback of our study is assessing neural involvement using only US, whereas there are some studies evaluating neuropathy with the contribution of electrophysiological and histological examinations. Not presenting the data regarding disease activity status of patients may constitute another limitation since low disease activity may be regarded as a reason for the lack of difference in CSAs. The small sample size may be viewed as a limitation; however, the participants were enrolled by a power analysis.

In conclusion, no difference was detected between RA patients without neuropathy symptoms and healthy volunteers in the CSA of the median and ulnar nerves. However, this result does not exclude the possibility of subclinical neuropathy in RA patients, which can be established by electrodiagnostic evaluation.

Ethics Committee Approval: The study protocol was approved by the Gazi University Faculty of Medicine Ethics Committee (date: 27.04.2011, no: 100). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: Ç.A.U., F.G.; Design: Ç.A.U., F.G., Z.G.; Control/supervision: Z.G., F.G.; Data collection and/or processing, writing the article: Ç.A.U., İ.S., Z.G.; Analysis and/or interpretation: Z.G., Ç.A.U., İ.S., F.G.; literature review: Ç.A.U., İ.S.; Critical review: Z.G., F.G.

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