Original article

Has the median nerve involvement in rheumatoid arthritis been overemphasized?

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ABSTRACT

Rheumatoid arthritis (RA) is a well and widely recognized cause of carpal tunnel syndrome (CTS). In the rheumatoid wrist, synovial expansion, joint erosions and ligamentous laxity result in compression of the median nerve due to increased intracarpal pressure. We evaluated the published studies to determine the prevalence of CTS and the characteristics of the median nerve in RA and its association with clinical parameters such as disease activity, disease duration and seropositivity. A total of 13 studies met the eligibility criteria. Pooled data from 8 studies with random selection of RA patients revealed that 86 out of 1561 (5.5%) subjects had CTS. Subclinical CTS, on the other hand, had a pooled prevalence of 14.0% (30/215). The cross sectional area of the median nerve of the RA patients without CTS were similar to the healthy controls. The vast majority of the studies (8/13) disclosed no significant relationship between the median nerve findings and the clinical or laboratory parameters in RA. The link between RA and the median nerve abnormalities has been overemphasized throughout the literature. The prevalence of CTS in RA is similar to the general population without any correlation between the median nerve characteristics and the clinical parameters of RA.

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O envolvimento do nervo mediano na artrite reumatoide tem sido excessivamente valorizado?

RESUMO

A artrite reumatoide (AR) é uma causa bem e amplamente reconhecida de síndrome do túnel do carpo (STC). No punho acemidado pela artrite reumatoide, a expansão sinovial, as erosões articulares e a frrouxidão ligamentar resultam em compressão do nervo mediano decorrente do aumento da pressão intracarpal. Avaliam-se os estudos publicados para determinar a prevalência de STC e as características do nervo mediano na AR e sua associação com parâmetros clínicos, como a atividade e duração da doença e a soropositivity.

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The abstracts of the studies were scrutinized for appropriate-ness before retrieving the full text of the articles. We searched the bibliographies of all relevant published articles to avoid missing other relevant studies. Fig. 1 summarizes the algorithm used for selection of the studies. Ethics approval was not required for this systematic review as there was no recruitment of subjects or research intervention.

Selection criteria

Inclusion criteria
The search was further refined to achieve a high level of homogeneity across the selected studies. We applied a time restriction to studies published from year 1980 onwards. We included studies about RA which:

1. examined the median nerve characteristics (sonographic and/or electrophysiological),
2. were about CTS,
3. were published in English.
Exclusion criteria
We excluded case reports and review articles. Studies on peripheral neuropathy which did not provide specific data on the median nerve were not considered either.

Data extraction
The following data were extracted from all studies included in this systematic review: study design, study population including details of the control arm, sample size, prevalence of CTS in RA, median nerve characteristics in RA (sonographic and electrophysiological), the relationship between the median nerve characteristics and the clinical parameters. The relevant and especially significant statistical values (p and r values) were recorded.

Results
A total of 13 studies
6,8–19 met the eligibility criteria. Majority of the studies (12/13) were cross-sectional, and there were 5 case-control studies.9,10,12,13,18 The controls employed by the studies were either healthy individuals9,10,13,18 or RA patients without symptoms of CTS.9 Study sample sizes varied from 2314 to 107016 subjects. Two of the studies11,14 dealt with subclinical CTS i.e. conducted among subjects without signs and symptoms of CTS. Tables 1 and 2 highlight the findings of the selected studies.

Prevalence of CTS in RA
In most studies, the diagnosis of CTS was based on a combination of symptoms (paraesthesia, tingling sensation, pain at the median nerve innervated area), signs (positive Tinel’s or Phalen test) and electrophysiological findings. The exact diagnostic criteria and definition of CTS used across the studies were quite diverse. Hammer et al.12 defined CTS based on a palm-to-wrist median sensory nerve action potential (SNAP) onset latency of >2.0 ms or absence of SNAP and median distal motor latency of >4.9 ms whereas Sim et al.18 defined CTS as a palm to wrist median nerve latency of less than 50%. The prevalence of CTS in RA ranged from 3.5%16 to 22.8%.17 Pooled data from 8 studies6,8,9,13,15–17,19 with random selection of RA patients revealed that 86 out of 1561 (5.5%) subjects had CTS. Subclinical CTS, on the other hand, had a pooled prevalence of 14.0% (30/215) (Table 2).

Sonographic findings of the median nerve in RA
Cross-sectional area (CSA) of the median nerve was determined using ultrasound scan in 3 of the studies.11–13 Two out of 3 of these studies12,13 were of case-control design with healthy individuals as controls. Hammer et al.11 investigated RA patients without signs and symptoms of CTS. The CSA of the bilateral median nerve of the RA patients without CTS were similar to the healthy controls. The mean (standard deviation) of the right median nerve in asymptomatic RA patients was 8.3 (1.5) mm² whereas for the left median nerve was 8.3 (1.4) mm².11 The CSA of the median nerve in CTS patients were significantly higher with a median of 15.7 mm² (11.1–21.8).12

Electrophysiological findings of the median nerve in RA
Electrophysiological assessment of the median nerve was carried out in 10/136,8,10,12,14–16,18,19 of the studies. Details of the NCS in terms of the median nerve velocity, amplitude and latency were provided only by 2 studies i.e. Lanzillito et al.10 and Calder et al.15 The former study reported that the median nerve sensory conduction velocity was reduced by 25.2% along the distal nerve segment in 57.5% of RA patients compared to the general population. The amplitude of the sensory responses was significantly reduced at the wrist and elbow in 17.5% and 5% of patients, respectively. Distal latency to the abductor pollicis brevis muscle was significantly slower in 10% of the patients whereas the maximum velocity from the elbow to the wrist was prolonged by 12% in almost a quarter of the subjects. Calder et al. found that the median nerve SNAP amplitude was significantly lower in the RA and hand osteoarthritis groups compared to the healthy controls (p = 0.05) but there were no appreciable differences in the median nerve SNAP conduction velocity and latency between the RA patients and the healthy controls. It is noteworthy that this study had an extremely small sample size with only 8 RA patients.

Correlation between the median nerve characteristics and the clinical parameters
Across the studies, the most frequently assessed clinical parameter was disease duration (9/13 studies) as compared to disease activity (4/13 studies).6,8,9,13 Apart from the above mentioned, the following clinical and laboratory parameters were commonly analyzed by the selected studies; age, height, weight, medications, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Approximately half of these studies were designed to compare the patients’ characteristics between RA patients with and without CTS11,16 or with and without neuropathy.6,8,17,18 The vast majority of the studies (8/13) disclosed no significant relationship between the median nerve involvement and clinical or laboratory parameters in RA. However, Karadag et al.13 and Biswas et al.9 revealed a significant association between disease duration and the occurrence of CTS (p = 0.036) and neuropathy (p = 0.001), respectively. Likewise, 2 studies found that age was significantly higher among RA patients with CTS13 and peripheral neuropathy.18

Discussion
Rheumatoid arthritis (RA) is often cited in the literature as one of the common etiologies of CTS. This systematic review, however, highlights, that the pooled prevalence of CTS in RA was 5.5% which did not differ significantly from the prevalence in the general population which ranged from 2.7 to 5.8%.20,21 We could have underestimated the prevalence in this regard as a sizable proportion (1070/1561) of the subjects included in the pooled analysis were from a retrospective study.6 Retrospective studies, in general, are notorious for underreporting due to missing or omitted data.22,23 In parallel with the aforementioned finding, our pooled prevalence of subclinical CTS of
Table 1 – Summary of the selected studies of CTS in RA.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Test(s)</th>
<th>Study population</th>
<th>Prevalence of CTS in RA n (%)</th>
<th>Clinical and laboratory parameters</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Lanzillo et al., 1998</td>
<td>NCS of peripheral nerves</td>
<td>40 RA patients</td>
<td>5 (12.5%)</td>
<td>Age, disease duration, steroid therapy, functional stage</td>
<td>The electrophysiologic findings were unrelated to clinical features of RA.</td>
</tr>
<tr>
<td>Sivri et al., 1999</td>
<td>NCS and somatosensory evoked potential studies</td>
<td>33 RA patients and 20 healthy controls</td>
<td>2 (6%)</td>
<td>No correlation between neuropathy and the clinical variables.</td>
<td></td>
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<tr>
<td>Sakini et al., 2005</td>
<td>NCS, EMG</td>
<td>80 RA patients</td>
<td>8 (22.8%)</td>
<td>Disease duration</td>
<td>There was no association between disease duration and the occurrence of neuropathy.</td>
</tr>
<tr>
<td>Hammer et al., 2006</td>
<td>US of the median nerves at the entrance of the carpal tunnel, NCS, Tinel's and Phalen's tests.</td>
<td>7 RA patients with CTS symptoms and with CTS symptoms</td>
<td>7 (14%)</td>
<td>Height, weight</td>
<td>CSA of the median nerves were significantly higher in the CTS patients compared with the RA controls and healthy persons; median (range) areas were 15.7 mm² (11.1–21.8), 8.5 mm² (5.8–11.0) and 8.0 mm² (4.9–12.0), respectively (p &lt; 0.0001). No significant correlation between CSA of median nerve and clinical parameters in the RA group. Healthy controls had significant correlation between CSA of median nerve and height (r = 0.6, p &lt; 0.001) and weight (r = 0.43, p = 0.001). Absence of deep tendon jerks (p &lt; 0.005) and vasculitis (p &lt; 0.01) were conspicuous in the neuropathic group. There was no relationship between neuropathy and other parameters.</td>
</tr>
<tr>
<td>Agarwal et al., 2008</td>
<td>NCS of peripheral nerves</td>
<td>108 RA patients</td>
<td>11 (10.1%)</td>
<td>Absence of deep tendon jerks, extra-articular manifestations (interstitial lung disease, vasculitis, subcutaneous nodules), disease duration, RF, joint erosions, joint deformities, DMARDs or glucocorticoid intake, and disease activity, abdominal fat pad for amyloid</td>
<td>Absence of deep tendon jerks (p &lt; 0.005) and vasculitis (p &lt; 0.01) were conspicuous in the neuropathic group. There was no relationship between neuropathy and other parameters.</td>
</tr>
<tr>
<td>Aktekin et al., 2009</td>
<td>EMG and NCS of the peripheral nerves</td>
<td>56 RA patients and 32 healthy controls</td>
<td>2 (4%)</td>
<td>Corticosteroid therapy, Schirmer's test, RF, disease activity</td>
<td>There was no correlation between electrophysiologic findings and the other study parameters. Disease duration and RF positivity was significantly higher in patients with neuropathy (p = 0.001 for both). No significant difference in other parameters between patients with and without neuropathy.</td>
</tr>
<tr>
<td>Biswas et al., 2011</td>
<td>NCS of the peripheral nerves</td>
<td>74 RA patients</td>
<td>3 (10.3%)</td>
<td>Age, disease duration, disease activity, RF, interstitial lung disease, subcutaneous nodules, vasculitis, corticosteroids, DMARDs and joint erosions</td>
<td></td>
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</table>
14.0% was within the reported range in the general population of 7–16%. 24

In healthy individuals, the mean CSA of the median nerve at the level of entrance into the carpal tunnel, which has the highest diagnostic sensitivity and specificity for CTS, has been found to be between 7.0 ± 1.0 mm² and 10.2 ± 2.5 mm². 25–27 The mean CSA of the median nerve in RA patients without signs and symptoms of CTS were similar to healthy controls. This lends credence to the notion that the chronic inflammatory processes in RA do not affect the size of the median nerve despite the close proximity between the median nerve and the wrist joint. However, Yagci et al. 28 had contradicting findings of RA patients having larger CSA of the median nerve despite absence of clinical and neurophysiological evidence of CTS.

No firm conclusions can be made on the electrophysiological changes of the median nerve in RA owing to the paucity of studies in this regard and the conflicting findings of the existing studies. Although Lanzillo et al. 15 revealed that more than half of RA patients without symptoms of CTS had reduced median nerve sensory conduction velocity along the distal nerve segment, this study failed to demonstrate any correlation between the clinical parameters of RA and the electrophysiological findings. Of note, this study had the drawback of not having a control arm and therefore, comparison was made with data from other published studies.

We found that there is no conclusive and convincing proof of association between the clinical or laboratory parameters in RA and the median nerve involvement. Although Karadag et al. 13 disclosed that age, disease duration and functional

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**Table 1 – (Continued)**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Test(s)</th>
<th>Study population</th>
<th>Prevalence of CTS in RA (%</th>
<th>Clinical and laboratory parameters</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Calder et al., 2012</td>
<td>NCS of the peripheral nerves, sensory mapping (SM), vibratory and current perception thresholds (VPT and CPT) of the 2nd and 5th digits</td>
<td>7 women with RA 9 healthy women 11 women with hand OA</td>
<td>126</td>
<td>All SNAP amplitudes were significantly lower for the hand OA and hand RA groups compared with the healthy group (p &lt; 0.05). No group differences were found for SNAP conduction velocities, SM, VFT, and CPT.</td>
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<tr>
<td>Karadag et al., 2012</td>
<td>Katz hand diagram, Boston CTS questionnaire, Phalen and Tinel tests. US of wrist joints and carpal tunnel gray scale and power Doppler. Patients with median nerve CSA between 10.0 and 13.0 mm² were evaluated with electromyography (EMG)</td>
<td>100 RA patients 45 healthy controls</td>
<td>126</td>
<td>Age, gender, body mass index, disease duration, goiter, disease activity, HAQ-DI, ESR, CRP, CTS global assessment, CTS symptom duration, Boston symptom severity score, Boston functional status</td>
<td>In RA group with CTS: age (57 [36–73] vs. 50 [24–76], p = 0.041), history of DM (35.5% vs. 6.0%, p &lt; 0.001), disease duration (108 [12–396] months vs. 72 [6–360] months, p = 0.036), HAQ-DI score (1.93 [0.75–2.87] vs. 1.13 [0–2.75], p = 0.013), CTS patient global score (52 [1–97] vs. 25 [0–91], p = 0.001), Boston symptom severity (2.81 [1.18–4.17] vs. 2.0 [1.0–4.01], p = 0.01) and functional status scores (3.37 [1.37–5.0] vs. 2.25 [1.0–5.0], p = 0.008) were elevated compared to patients without CTS. The mean ages of the patients with and without peripheral neuropathy were 69.4 and 56.5 years, respectively (p &lt; 0.05).</td>
</tr>
<tr>
<td>Sim et al., 2014</td>
<td>NCS, Neuropathic Symptoms Scale (NSS)</td>
<td>30 RA patients with symptoms of peripheral neuropathy</td>
<td>126</td>
<td>Age, anti-CCP, the type of medication, disease duration, functional status, neuropathic symptoms, ESR, CRP</td>
<td>There was no statistically significant correlation between CTS occurrence and duration of RA and CRP levels.</td>
</tr>
<tr>
<td>Lee et al., 2015</td>
<td>EMG, NCS, Phalen’s and Tinel’s tests</td>
<td>1070 RA patients</td>
<td>126</td>
<td>CRP, disease duration</td>
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EMG, electromyography; NCS, nerve conduction studies; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CTS, carpal tunnel syndrome; RA, rheumatoid arthritis; HAQ-DI, Health Assessment Questionnaire–disability index; OA, osteoarthritis; DMARD, disease modifying antirheumatic drug.
scores were higher among the RA patients with CTS, the remaining studies were not in agreement with the above findings. However, numerous studies which investigated the extra-articular manifestations of RA, in general, identified the following factors as predictors in this regard: high disease activity, smoking, antinuclear antibodies and rheumatoid nodules.29,30

The studies included in this systematic review were not without their individual limitations. In particular, many had a small sample size, hence limiting the statistical power. Many of the studies did not fully control for confounding factors of CTS such as occupation, the presence of diabetes mellitus and hypothyroidism. Definition of CTS varied substantially across the studies. Misclassification as CTS, particularly among studies that diagnosed CTS solely based on symptoms, was another potential source of error. In conclusion, the nexus between RA and the median nerve abnormalities or CTS has been overemphasized throughout the literature. Based on this systematic review, a substantial body of research suggests that the prevalence of CTS in RA is similar to the general population without any correlation between the median nerve findings and the clinical parameters of RA.

### Conflicts of interest

The authors declare no conflicts of interest.

### Acknowledgements

The author would like to thank the librarians of “Universiti Kebangsaan Malaysia” for their assistance in retrieving the full text of the articles.

### References

12. Hammer HB, Hovden IA, Haavardsholm EA, Kvien TK. Ultrasonography shows increased cross-sectional area of the

### Table 2 – Summary of the selected studies of subclinical CTS in RA.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Test(s)</th>
<th>Study population</th>
<th>Prevalence of subclinical CTS in RA n (%)</th>
<th>Clinical and laboratory parameters</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Lang et al., 1981</td>
<td>NCS of 6 sensory nerves</td>
<td>23 RA patients</td>
<td>5 (21.7%)</td>
<td>Age, gender, disease duration,</td>
<td>No significant correlation between neurophysiological/neurological</td>
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<td>stage of disease, RF, ESR.</td>
<td>findings and other study parameters.</td>
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<td>Height, weight, age, gender,</td>
<td>The CSA of the median nerves ranged from 5.0 to 12.8 mm², with</td>
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<td>disease duration, use of</td>
<td>the 97.5 centile being 11.1 mm².</td>
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<td>prednisolone.</td>
<td>The mean cross-sectional areas of the median nerve in patients with RA</td>
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<td>were similar to those reported in healthy controls.</td>
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<td>No significant association between CSA of median nerve and all studied</td>
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<td>parameters except for gender; males were significantly higher (8.8 ± 1.3</td>
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<td>mm² versus females: 8.0 ± 1.4 mm² [p, 0.001]</td>
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<tr>
<td>Hammer et al., 2007</td>
<td>US of the median nerves at the</td>
<td>154 RA patients</td>
<td>10%</td>
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<td>entrance of the carpal tunnel</td>
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NCS, nerve conduction studies; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CTS, carpal tunnel syndrome; RA, rheumatoid arthritis.