Foot neuropathy in rheumatoid arthritis patients: clinical, electrophysiological, and ultrasound studies

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Aim
This study aimed to evaluate neuropathic foot pain in patients with rheumatoid arthritis (RA) using electrophysiological studies and musculoskeletal ultrasound (MSUS) to address the association between these findings and disease activity. Evaluation of the usefulness of this combination was undertaken.

Design
The present study was designed as a cross-sectional study.

Patients and methods
A total of 50 RA patients underwent a complete history-taking and rheumatologic examination. According to the cut-off point of Disease Activity Score in 28 joints, patients were divided into two equal groups (25 patients each): active and inactive. In total, 25 healthy individuals were included as controls. Routine tibial and peroneal nerve conduction studies, as well as electromyography of tibialis anterior and abductor hallucis muscles, were carried out. MSUS assessment of the ankle joint and extra-articular portion of the foot complex was also performed.

Results
Electrophysiological findings of foot neuropathy were observed in 78% of the patients, irrespective of the disease activity level. In total, 48% of the patients had mononeuropathies of a demyelinating pattern (entrapment neuropathies), whereas the other 30% had symmetrical polyneuropathy with axonal degeneration. Combined distal tibial and peroneal nerve entrapments were reported in 16% of the patients. A positive power Doppler signal and joint erosions showed a highly statistical significant prevalence among the active group in comparison with patients in remission ($P \leq 0.001$).

Conclusion
Peripheral nerve affection is common in the rheumatoid foot, irrespective of the disease activity status. The most common neuropathies were posterior tarsal tunnel syndrome, peroneal nerve entrapment at the fibular neck, and pure sensory axonal neuropathy. A positive power Doppler signal and bone erosions of the ankle joint, detected by MSUS, were associated with RA disease activity. Electrophysiology was superior to MSUS for the diagnosis of posterior tarsal tunnel syndrome.

Keywords:
musculoskeletal ultrasound, neuropathic pain, rheumatoid foot

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic rheumatic inflammatory disorder predominantly affecting synovial joints. The inflammatory response within the joint synovium leads to joint erosion, ligament laxity, and subsequent deformity. In addition, extra-articular manifestations occur in 10–20% of patients, especially those with high titers of rheumatoid factor. Extra-articular pathology includes bursitis, tendonitis, fasciitis, neuritis, and vasculitis [1,2].

Clinical involvement of the peripheral nervous system may be asymptomatic in the early stages of the rheumatoid disease or may present with a wide variety of symptoms such as pain, paresthesias, and muscle weakness. These symptoms may mimic and overlap with those of arthritis [3]. In presence of severe joint disease, restriction, pain, and deformities, symptoms of neuropathy may be overlooked or overestimated [2,4].

For persons with RA, the prevalence of foot pain has been reported in varying numbers within the published literature [5]. Although patients with RA complain of foot pain and disability because of foot problems, physicians generally overlook or neglect the feet in

routine clinical examination. This is because feet and ankles are not included as part of the Disease Activity Scoring in 28 joints (DAS28) scoring system, which is generally used to assess disease activity and helps to define clinical remission of the disease. Hence, patients in remission may suffer from foot disease activity, as shown in the previous studies [6].

Evaluation mainstays of the rheumatoid foot include both electrophysiological and imaging techniques [2]. Musculoskeletal ultrasound (MSUS) is an attractive method of imaging because of its low cost, absence of harmful radiation, and rapidity of imaging. Compared with standard radiography, ultrasonography (US) is shown to be superior at detecting joint erosions early in the course of the disease. In addition, it can study tendon involvement, which often accompanies and in some cases precedes the evidence of the disease at the joint level [2,7].

This study aimed to evaluate neuropathic foot pain in patients with RA using electrophysiological studies and MSUS to address the association between these findings and disease activity. Electrophysiology was used to assess the peripheral electrophysiological changes in the rheumatoid feet, whereas MSUS was used to assess bone erosions and synovitis in these patients. Evaluation of the usefulness of this combination was undertaken.

Patients and methods

After the approval of the protocol from our ethical committee and after providing detailed information to the patients as regards the aim and procedures of the study, 50 patients with RA having neuropathic pain in their feet gave their consent and were then enrolled in this study. The patients were recruited from the Physical Medicine & Rehabilitation Clinic, Menoufia University Hospitals.

RA was diagnosed according the 2010 ACR/EULAR criteria for classification of RA [8]. Characteristics of neuropathic pain described by the patients included in the study were burning; painful, cold sensations or electric shocks possibly associated with tingling, pins, and needles; numbness; or itching [9].

Patients were excluded if they had diabetes mellitus, L5 and S1 radiculopathies, space occupying lesions at the tarsal tunnel, foot trauma and fractures, congenital or post-traumatic foot deformity, varicose veins and deep venous thrombosis, severe obesity by BMI or lower limb edema. Moreover, patients with peripheral neuromyopathy or arthritis due to systemic or local disease 'other than RA' or drug-induced were not included in our study.

According to the cut-off point of the DAS28 [10], the patients were divided into two groups: group I (active RA) and group II (inactive RA). Group III constituted the healthy controls, 25 in number.

All the patients were subjected to a detailed history-taking. Assessment of foot function was carried out using the Swindon Foot and Ankle Questionnaire (SFAQ), which is a simply worded 10-point foot-and-ankle screening questionnaire with diagrams for rapid screening in routine rheumatology outpatients [11]. Assessment of functional disability was performed using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI), which consists of eight questions regarding the limitations that the patients experience in performing daily physical activities [12].

Complete rheumatologic examination was carried out for every participant, including neurological examination of the four extremities with special emphasis on excluding upper motor neuron lesions or lesions affecting any part of the lower motor neuron pathway other than the peripheral nerves. Moreover, saphenous neuropathy, sciatic neuropathy and proximal affection of tibial, and common peroneal nerves were excluded.

In this study, the Medical Research Council grading scale (0–5) was used for muscle strength assessment [13]; muscle weakness was assumed to be present if any muscle in the lower limb has a score less than 5. Abnormal muscle mass index indicated muscle wasting [14]. Eliciting Tinel's sign was considered as an objective clinical sign for possible tibial or peroneal nerve entrapments [2,15]. In addition, superficial sensations using a pinprick were examined and an altered pinprick response was used to infer a possible neuropathic pain [16].

Electrophysiological testing

All 50 patients along with the controls were tested by the Neuropack M1 electromyograph (EMG) apparatus (Nihon Kohden, Tokyo, Japan). Nerve conduction (motor and sensory) studies were conducted on bilateral medial plantar, lateral plantar, deep peroneal, superficial peroneal, and sural nerves. Needle EMG was also performed bilaterally on the tibialis anterior and abductor hallucis muscles. This was done as described in a study by Kim and colleagues [17–24]. Findings were presented as the mean value of both sides.

It was proposed that abnormal sural and/or peroneal sensory responses along with any abnormalities in the plantar nerves were likely secondary to a polyneuropathy [22]. Diagnosis of posterior tibial nerve entrapment at the ankle was based on measuring the distal motor latency and distal sensory latency of both medial and lateral plantar nerves as well as their compound muscle action potential and sensory nerve action potential amplitudes. Calculated cut-off points of the electrophysiological parameters were used. It was proposed that the affection of any parameter of the electrophysiological study reflects pathologic affection of the related nerve [22,25]. Finally, diagnosis of peroneal nerve entrapment at the fibular neck was based on certain neurophysiological criteria:

(i) Demyelinating lesion,
(ii) Compound muscle action potential axonal damage,
(iii) Mixed involvement (conduction block plus axonal damage), and
(iv) Sensory nerve action potential axonal loss [26–28].

Musculoskeletal ultrasound testing

A commercially available real-time scanner (Hitachi Medical Systems, Tokyo, Japan) was used for the US examination using a multilinear high-frequency (10 MHz) linear array transducer. The patients underwent systematic multiplanar, bilateral and dynamic gray-scale US and Power Doppler ultrasound (PDUS) assessments of the ankle joint and the extra-articular portion of foot complex, as described by Riente *et al*. [29].

The ankle joint was evaluated in both transverse and longitudinal planes, regarding three criteria: synovitis, power Doppler (PD) signal, and erosions.

Joint synovitis, which was detected by gray-scale US, was defined as the presence of synovial hypertrophy and/or intra-articular effusion. Active synovitis was defined as intra-articular synovitis detected with PD signal [30]. Intra-articular PD activity was evaluated using a semiquantitative four-grade scale of 0–3 [31,32]. According to OMERACT guidelines, joint erosion was defined as intra-articular discontinuity of the bone surface, which was visible in two perpendicular planes [33]. Erosions were recorded as either present or absent.

Diagnosis of tarsal tunnel syndrome (TTS) was based on detection of anatomically relevant changes of the tarsal tunnel, associated with RA, mainly signs of active inflammation affecting soft tissue within the tunnel: tenosynovitis/synovial hypertrophy with or without effusion, tendinitis, paratenonitis, as well as bursitis with effusion and/or synovial hypertrophy [2].

The current study faced multiple technical considerations for sonography of the posterior tibial and deep peroneal nerves at their tunnels as a 10 MHz probe was used, whereas superficially located nerves such as the median nerve, ulnar nerve, peroneal and tibial nerves should be examined with transducers of 15–18 MHz [34].

Statistical methods

Statistical analyses were performed with SPSS 20 for Windows (SPSS Inc., Chicago, Illinois, USA). For continuous variables, Mann–Whitney *U*-test or independent-sample Student's *t*-test was used for comparison between two groups. For comparison between three groups, one-way ANOVA test or Kruskal–Wallis test was used. For categorical variables, χ^2-test was used. In addition, bivariate regression analysis (*r*-test) was performed to assess the independent association between the nerve conduction study (NCS)/EMG variables and disease activity in each patient group. A *P*-value of less than or equal to 0.05 was considered statistically significant and a *P*-value of less than or equal to 0.001 was considered highly statistically significant.

Results

Demographic and clinical characteristics

A total of 50 patients and 25 controls were enrolled in the present study. Demographic data are presented in Table 1. It shows that there was a significant prevalence of muscle weakness and wasting among patients in group I when compared with group II patients. An altered pinprick response, in the form of mechanical allodynia and/or hyperalgesia/hypoalgesia, showed no significant relationship between this deficit and disease activity ($P > 0.05$). It was found in 37 (74%) patients; 30 (60%) patients showed a bilateral deficit, whereas the other seven (14%) patients showed a unilateral deficit.

Finally, there was a highly significant prevalence of increased SFAQ and Stanford HAQ-DI scores ($P = 0.001$) among patients in group I when compared with group II patients (Table 1).

Nerve conduction studies and needle electromyography findings

Table 2 compares NCSs parameters among the studied groups (groups I, II, and III), which revealed significant

Table 1 Characteristics of patients in the studied groups

Patient characteristics	Group I (*n* = 25)	Group II (*n* = 25)	Group III (*n* = 25)	*P*-value
Age (mean ± SD) (years)	42.40 ± 8.31	37.20 ± 6.80	37.44 ± 11.57	0.082
Disease duration (mean ± SD) (years)	10.36 ± 6.2	7.60 ± 4.34	–	0.131
Sex [*N* (%)]				0.321
Female	23 (92)	23 (92)	20 (80)	
Male	2 (8)	2 (8)	5 (20)	
Weakness [*N* (%)]				0.023 (S)
Present	18 (72)	10 (40)	–	
Absent	7 (28)	15 (60)	–	
Wasting [*N* (%)]				0.037 (S)
Present	4 (16)	0 (0)	–	
Absent	21 (84)	25 (100)	–	
Altered pinprick response [*N* (%)]				0.747
Present	19 (76)	18 (72)	–	
Absent	6 (24)	7 (28)	–	
Tinel's sign [*N* (%)]				0.208
Present	13 (52)	17 (68)	–	
Absent	12 (48)	8 (32)	–	
SFAQ score (mean ± SD)	6.52 ± 1.01	5.28 ± 1.46	–	0.001 (HS)
HAQ-DI score (mean ± SD)	0.59 ± 0.25	0.25 ± 0.3	–	0.000 (HS)

Group I, active RA; group II, inactive RA; and group III, controls, HAQ-DI, Health Assessment Questionnaire Disability Index; HS, highly significant ($P \leq 0.001$); RA, rheumatoid arthritis; S, significant ($P \leq 0.05$); SFAQ, Swindon Foot and Ankle Questionnaire.

Table 2 Nerve conduction study results in the studied groups

NCS parameters	Group I (*n* = 25)[a]	Group II (*n* = 25)[b]	Group III (*n* = 25)	*P*-value
Medial plantar DML (mean ± SD) (ms)	3.74 ± 0.68	3.94 ± 0.97	3.36 ± 0.67	0.034 (S)
Tibial MCV (mean ± SD) (m/s)	43.06 ± 3.64	43 ± 3.57	46.45 ± 3.28	0.001 (HS)
Lateral plantar DML (mean ± SD) (ms)	5.19 ± 0.60	5.63 ± 0.99	4.71 ± 0.41	0.000 (HS)
Lateral plantar CMAP amplitude (mean ± SD) (mV)	6.51 ± 2.95	8.23 ± 3.94	8.92 ± 2.58	0.021 (S)
Deep peroneal DML (mean ± SD) (ms)	3.94 ± 0.93	4.04 ± 0.65	4.48 ± 0.84	0.049 (S)
Deep peroneal CMAP amplitude (mean ± SD) (mV)	2.79 ± 1.29	3.23 ± 1.34	3.84 ± 0.92	0.016 (S)
Sural DSL (mean ± SD) (ms)	3.11 ± 0.57	3.04 ± 1.08	3.50 ± 0.09	0.000 (HS)
Sural SNAP amplitude (mean ± SD) (μV)	8.99 ± 3.16	10.75 ± 5.66	15.12 ± 6.15	0.002 (S)
Peroneal SNAP amplitude (mean ± SD) (μV)	8.49 ± 2.86	12.43 ± 3.84	18.27 ± 4.89	0.000 (HS)
Medial plantar DSL (mean ± SD) (ms)	6.62 ± 2.11	3.10 ± 0.081	3.17 ± 0.35	0.000 (HS)
Lateral plantar DSL (mean ± SD) (ms)	6.48 ± 1.72	3.28 ± 0.13	3.19 ± 0.28	0.000 (HS)

Group I, active RA; group II, inactive RA; group III: control, CMAP, compound muscle action potential; DML, distal motor latency; DSL, distal sensory latency; HS, highly significant ($P \leq 0.001$); MCV, motor conduction velocity; NCS, nerve conduction study; RA, rheumatoid arthritis; S, significant ($P \leq 0.05$); SNAP, sensory nerve action potential, [a]Number of obtainable sensory responses for group I was as follows: 22 for the sural nerve, 20 for the superficial peroneal nerve, 10 for the medial plantar nerve, and 8 for the lateral plantar nerve, [b]Number of obtainable sensory responses for group II was as follows: 17 for the sural nerve, 17 for the superficial peroneal nerve, 7 for the medial plantar nerve, and 5 for the lateral plantar nerve.

($P \leq 0.05$) to a highly significant ($P \leq 0.001$) changes in the motor and sensory nerve studies regarding mean values of distal latency, amplitude, and conduction velocity in RA patients compared with healthy indivisuals.

Table 3 displaying results of the needle EMG in the studied muscles reveals that the motor unit action potentials (MUAPs) showed a significant ($P \leq 0.05$) to a highly significant ($P \leq 0.001$) reduction in the duration and amplitude among the patients in comparison with the controls. It also shows a highly significant increased proportions of spontaneous activity recorded from abductor hallucis muscle in patients compared with controls ($P \leq 0.001$). However, the intrinsic foot muscles commonly show increased insertional activity and occasionally fibrillation potentials associated with large, long-duration MUAPs, as one would expect in a neurogenic lesion. Such findings are not unusual in normal indivisuals without symptoms, however, and are thought to be due to everyday wear and tear of the feet [22].

Table 4 of bivariate correlation analyses between the nerve study parameters or MUAP parameters on one side and DAS28 on the other side showed insignificant results ($P > 0.05$), except for the distal sensory latency and sensory nerve action amplitude of the medial plantar response, being significant in group II patients ($P \leq 0.05$). However, this significant finding cannot be

Table 3 Needle electromyography results in the studied groups

EMGs	Group I (n = 25)[a]	Group II (n = 25)[b]	Group III (n = 25)	P-value
MUAP duration (TA) (mean ± SD) (ms)	7 ± 2.02	8.15 ± 1.97	8.56 ± 2.20	0.026 (S)
MUAP amplitude (TA) (mean ± SD) (μV)	0.40 ± 0.15	0.49 ± 0.29	0.88 ± 0.53	0.002 (S)
Spontaneous activity (AH) [N %)]	0 (0)	6 (24)	0 (0)	0.001 (HS)
MUAP duration (AH) (mean ± SD) (ms)	6.38 ± 2.50	6.69 ± 1	8.56 ± 2.20	0.001 (HS)
MUAP amplitude (TA) (mean ± SD) (μV)	0.56 ± 0.47	0.41 ± 0.21	0.79 ± 0.42	0.004 (S)

Group I, active RA; group II, inactive RA; group III: control, AH, abductor hallucis; EMG, electromyograph; HS, highly significant ($P \leq 0.001$); MUAP, motor unit action potential; RA, rheumatoid arthritis; S, significant ($P \leq 0.05$); TA, tibialis anterior.

Table 4 Correlation coefficients (r) between Disease Activity Score in 28 joints and nerve conduction study/electromyographic results, in the patients' groups

NCS/EMG parameters	Disease Activity Score in 28 joints			
	Group I (n = 25)[a]		Group II (n = 25)[b]	
	r-Test	P-value	r-Test	P-value
Medial plantar n. DML	−0.364	0.073 (NS)	0.069	0.742 (NS)
Lateral plantar n. DML	0.036	0.864 (NS)	−0.108	0.608 (NS)
Peroneal n. DML	0.089	0.671 (NS)	0.390	0.054 (NS)
Sural n. DSL	−0.263	0.237 (NS)	0.059	0.823 (NS)
Peroneal n. DSL	0.316	0.174 (NS)	0.08	0.761(NS)
Medial plantar n. DSL	0.589	0.073 (NS)	0.811	0.027 (S)
Lateral plantar n. DSL	0.388	0.342 (NS)	−0.315	0.606 (NS)
Medial plantar n. CMAP amplitude	0.202	0.333 (NS)	−0.380	0.061 (NS)
Lateral plantar n. CMAP amplitude	0.128	0.541 (NS)	−0.353	0.083 (NS)
Peroneal n. CMAP amplitude	−0.138	0.512 (NS)	−0.275	0.184 (NS)
Sural n. SNAP amplitude	−0.291	0.189 (NS)	−0.399	0.113(NS)
Peroneal n. SNAP amplitude	−0.370	0.109 (NS)	0.370	0.144 (NS)
Medial plantar n. SNAP amplitude	0.079	0.829 (NS)	−0.759	0.048 (S)
Lateral plantar n. SNAP amplitude	−0.026	0.951 (NS)	0.032	0.959 (NS)
Tibial n. motor conduction velocity	0.192	0.359 (NS)	−0.265	0.200 (NS)
Peroneal n. motor conduction velocity	−0.058	0.784 (NS)	−0.256	0.216 (NS)
MUAP duration of TA m.	0.048	0.821 (NS)	0.115	0.584 (NS)
MUAP amplitude of TA m.	0.139	0.509 (NS)	0.327	0.111 (NS)
MUAP duration of AH m.	−0.194	0.353 (NS)	−0.179	0.393 (NS)
MUAP amplitude of TA m.	−0.383	0.059 (NS)	−0.181	0.387 (NS)

Group I, active RA; group II, inactive RA, AH, abductor hallucis; CMAP, compound muscle action potential; DML, distal motor latency; DSL, distal sensory latency; m., muscle; MUAP, motor unit action potential; n, nerve; RA, rheumatoid arthritis; S, significant ($P \leq 0.05$); SNAP, sensory nerve action potential; TA, tibialis anterior, [a]Number of obtainable sensory responses for group I was as follows; 22 for the sural nerve, 20 for the superficial peroneal nerve, 10 for the medial plantar nerve, and 8 for the lateral plantar nerve, [b]Number of obtainable sensory responses for group II was as follows; 17 for the sural nerve, 17 for the superficial peroneal nerve, 7 for the medial plantar nerve, and 5 for the lateral plantar nerve.

relied upon on the basis of the few obtainable plantar sensory responses, and thus being a marked limitation in this study.

Table 5 shows the prevalence of the electrophysiological patterns in the patient's groups. Out of 50 patients, 39 (78%) had different types of peripheral neuropathy, 24 (48%) had mononeuropathies of demyelinating pattern (entrapment neuropathies), and 15 (30%) had symmetrical polyneuropathy with axonal degeneration.

Figure 1 shows the prevalence of electrophysiological findings of peripheral neuropathy in the patients' groups. The most common type of neuropathy which was observed was pure sensory axonal neuropathy (24% of the patients) followed by tibial nerve entrapment at posterior tarsal tunnel 'posterior TTS' (20% of the patients), combined entrapments of posterior tibial nerve at the ankle and peroneal nerve at fibular neck (16% of the patients), peroneal nerve entrapment at fibular neck (12% of the patients), and finally sensorimotor axonal neuropathy (6% of the patients). None of the studied cases showed deep peroneal nerve entrapment at the ankle, pure motor axonal neuropathy or mononeuritis multiplex.

Table 6 shows that posterior tibial nerve entrapment at the ankle was reported in 18 (36%) patients; 10 (20%) patients showed an isolated tibial nerve affection and eight (16%) patients had an associated peroneal nerve entrapment at the fibular neck. It also reveals that peroneal nerve entrapment at the fibular neck was reported in 14 cases (28% of cases); six cases had an

isolated peroneal nerve affection and eight cases had an associated posterior tibial nerve entrapment at the ankle.

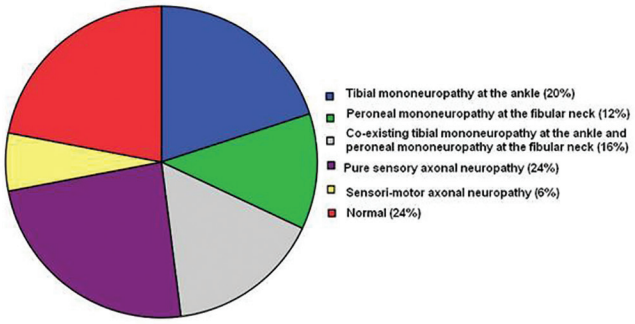
Musculoskeletal ultrasound findings

Figures 2 and 3 show the results of PDUS and joint erosion assessment of the ankle joint, respectively. There was a highly statistically significant prevalence of positive ankle PD signal and joint erosions among group I patients in comparison with group II patients ($P \leq 0.001$).

The comparison between electrophysiological and ultrasonograhic diagnoses of posterior tarsal tunnel syndrome

This comparison, as displayed in Table 7, revealed statistically significant results ($P < 0.05$), according to which electrophysiology could detect the syndrome in 18 (36%) patients, whereas MSUS could detect the syndrome in only eight (16%) patients.

Figure 1



The prevalence of electrophysiological findings of peripheral neuropathy in the patients' groups ($n = 50$).

Table 5 Prevalence of the electrophysiological patterns and findings in the patients' groups ($n = 50$)

Electrophysiological patterns	Frequency [*N* (%)]
Demyelinating mononeuropathy (entrapment neuropathies)	24 (48)
Symmetrical axonal polyneuropathy	15 (30)
Mononeuritis multiplex (multiple mononeuropathy)	0 (0)
Total cases of peripheral neuropathy	39 (78)

Discussion

The present study showed that females and males constituted 92 and 8%, respectively, in both the patients' groups, whereas female to male ratio was 80 to 20%, respectively, in the control group. This emphasizes the higher prevalence of RA in females than in males, whereas the sex ratio is typically around 3 : 1 [35,36].

There was a significant prevalence of muscle weakness among the active RA group when compared with the inactive one ($P \leq 0.05$). There was a significant positive association ($P \leq 0.05$) between the disease activity score and isometric muscle strength, which was measured with the validated Muscle Strength Index [37,38]. Muscle weakness is generally attributed to a reflex response to pain, joint deformation or disuse, extra-articular manifestations of the disease and/or psychological factors [39].

Similarly, there was a significant prevalence of muscle wasting among the active RA patients when compared with the inactive group ($P \leq 0.05$). This confirms what other authors found that DAS28 score is negatively correlated with the lean body cell mass [40,41].

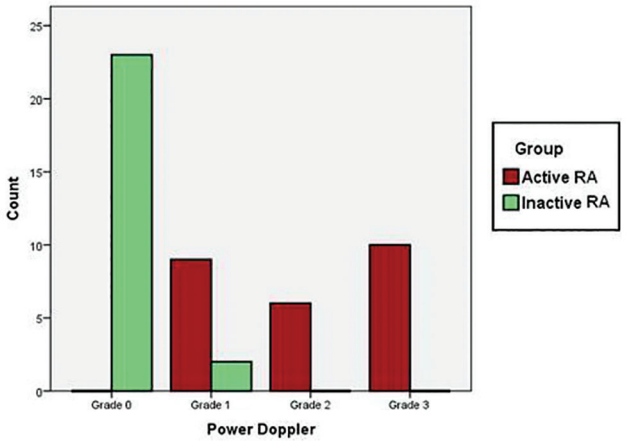
Mechanical allodynia and/or hyperalgesia/hypoalgesia were assumed to be pathognomonic of neuropathic pain [16]. In our study, an altered pinprick response was found in 30 (60%) patients bilaterally and in seven (14%) patients unilaterally.

A highly significant SFAQ scoring ($P \leq 0.001$) was encountered more among the active patients than among the inactive ones. This disagrees with the study conducted by Waller *et al.* [11], which reported that the SFAQ did not correlate with DAS28. However, a limitation of both studies, Waller's research and the present study, is that feet and ankles are not included as part of the DAS28 scoring system.

Table 6 Frequency of affection of the plantar and peroneal nerves in posterior tibial and peroneal entrapments in the patients' groups ($n = 50$)

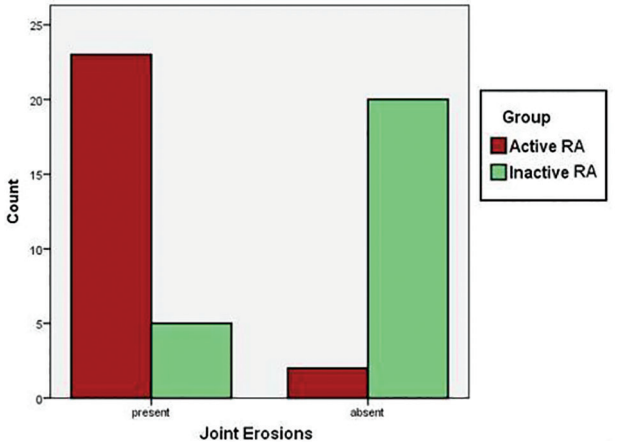
Nerves affected	Distribution	Frequency [*N* (%)]
Posterior tibial nerve entrapment at the ankle	Total cases	18 (36)
	Isolated medial plantar nerve affection	0 (0)
	Isolated lateral plantar nerve affection	10 (20)
	Both medial and lateral plantar nerves affection	8 (16)
Peroneal nerve entrapment at the fibular neck	Total cases	14 (28)
	Isolated superficial peroneal nerve affection	0 (0)
	Isolated deep peroneal nerve affection	4 (8)
	Both superficial and deep peroneal nerves affection	10 (20)

Figure 2



Power Doppler findings in the patients' groups (n = 50). RA, rheumatoid arthritis.

Figure 3



Joint erosions in the patients' groups (n = 50). RA, rheumatoid arthritis.

Table 7 Comparison between electrophysiological and ultrasound diagnoses of posterior tarsal tunnel syndrome

Ultrasound diagnosis [*N* (%)]	Electrophysiological diagnosis [*N* (%)]	Test of significance (χ^2-test)	*P*-value
8 (16)	18 (36)	2.05	0.04 (S)

S, significant ($P \leq 0.05$).

Similarly, a highly significant HAQ-DI was encountered more among the active patients than among the inactive ones ($P \leq 0.001$). Keeping-up with our results, previous studies found a significant correlation between HAQ-DI and DAS28 in RA patients [42–44], suggesting that functional incapacity is most associated with disease activity in early RA [42].

NCSs parameters among the studied groups represented the preliminary changes of neuropathic lesions in RA patients, which were previously reported in the literature in the form of significant affection of nerve study parameters of the median, ulnar, peroneal, and posterior tibial nerves in RA patients compared with controls [45–47].

Regarding the needle EMG findings in this study, the reduction of MUAP duration and amplitude, associated with polyphasia, is suggestive of a state of early reinnervation following severe denervation, or it may suggest a concomitant myopathy. Many [46,48,49] case–controlled studies that involved EMG examination of different muscles in RA patients had been conducted previously. The studied muscles showed neuropathic interference pattern, definite signs of neuropathy or definite signs of denervation [46].

In general, findings confirm the prevalence of neuropathy in RA. This was in agreement with the studies conducted by Olney [50], Kadhim *et al.* [46], and Agarwal *et al.* [3], which concluded that neuropathies are common in patients with diffuse connective tissue diseases.

Accordingly, the current study assumes that there is no relationship between rheumatoid neuropathy and disease activity status. In agreement with our results, previous research work stated that rheumatoid neuropathy occurs irrespective of the disease activity level [3,51,52]. High disease activity was not stated as a predictor of rheumatoid vasculitis [53]. Moreover, entrapment neuropathies are associated with mechanical nerve compression as a result of local joint changes, including swelling of soft tissues, synovitis, tenosynovitis, bone erosions joint deformity or rheumatoid nodules [54–56]. Moreover, there is no correlation between compression neuropathies and the level of acute phase reactants [57].

The prevalence of rheumatoid neuropathy vary among previous studies [3,51,58–61]. The electrophysiological findings of mild distal symmetric pure sensory and combined sensorimotor axonal neuropathies contribute to the clinical presentation of distal sensory neuropathy (DSN). This emphasizes the prevalence of DSN in RA patients. Rheumatoid diseases are one of the most common causes of DSN [62].

An important observation provided by the current study was the coexistence of posterior tibial nerve entrapment at the ankle and peroneal nerve entrapment at the fibular neck. According to our knowledge, no previous studies have addressed this issue.

In this study, the electrophysiological diagnosis of posterior TTS was encountered in 18 (36%) patients. Baylan's study examined 48 RA patients for the

presence of posterior TTS and found that 11 (25%) patients had a definite delay in the distal motor latency of the tibial nerve [63]. Moreover, Ibrahim *et al*. [2] documented the electrodiagnosis of posterior TTS in 28 out of the 30 feet of RA patients.

The electrophysiological findings of peroneal nerve entrapment at the fibular neck may be due to the compression of the nerve by a ganglion, rheumatoid nodule, an extension of synovial hypertrophy from the knee or even a large knee osteophyte [64]. Data about incidence and prevalence of peroneal neuropathy in rheumatoid knees are insufficient. An increased peroneal neuropathy at the fibular head has been reported in RA [65].

Lateral plantar nerve was found to be more affected than medial plantar nerve in the patients with TTS. It was previously stated that the lateral plantar nerve is probably affected earlier than the medial plantar one [25]. In another study performed on RA patients, none of the patients showed isolated medial plantar nerve affection [2].

Similarly, none of the patients who were diagnosed with peroneal nerve entrapment at the fibular neck showed isolated superficial peroneal nerve lesion. It was reported that the superficial peroneal nerve is usually less involved than is the deep peroneal nerve [66]. The most likely explanation was the selective vulnerability of different nerve fascicles to injury, which leads to differing degree of damage to individual fascicles within the common peroneal nerve [67].

A positive PD signal and joint erosions are considered to be associated with diseased activity on the basis of their prevalence in the active patients when compared with the inactive ones ($P \leq 0.001$). Keeping-up with our results, a previous study displayed similar ankle PD findings [68]. The microstructural bone changes associated with development of bone erosions in RA seem to be closely related to disease activity. Explanation for this finding was that disease activity is closely associated to presence of hypervascularity (PD changes), further contributing to the development of erosions and other forms of structural damage [69].

On comparing electrophysiological and US diagnoses of posterior TTS, electrophysiological studies were able to detect more cases of posterior TTS ($P < 0.05$). Electrophysiology could detect the syndrome in 18 (36%) patients, whereas MSUS could detect the syndrome only in eigth (16%) patients. Similar findings were reported by Ibrahim *et al*. [2] who investigated for posterior TTS in 30 rheumatoid feet. Electrophysiologically, they could detect 28 (93.3%) patients, whereas by MSUS only 10 (33.3%) patients could be detected. This supports the evidence that electrophysiology is the test of choice for confirming the diagnosis of posterior TTS in 90–100% of cases [62,70–75].

Conclusion

Peripheral nerve affection is common in the rheumatoid foot, irrespective of the disease activity status. The most common neuropathies were posterior TTS, peroneal nerve entrapment at the fibular neck, and pure sensory axonal neuropathy. A positive PD signal and bone erosions of the ankle joint, detected by MSUS, were associated with RA disease activity. Electrophysiology was superior to MSUS for the diagnosis of posterior TTS.

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Conflicts of interest

There are no conflicts of interest.

References

1 Loveday DT, Jackson GE, Geary NP. The rheumatoid foot and ankle: current evidence. Foot Ankle Surg 2012; 18:94–102.

2 Ibrahim I, Medani S, El-Hameed M, Imam M, Shaaban M. Tarsal tunnel syndrome in patients with rheumatoid arthritis, electrophysiological and ultrasound study. Alexandria J Med 2013; 49:95–104.

3 Agarwal V, Singh R, Wiclaf, Chauhan S, Tahlan A, Ahuja C, *et al.* A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol 2007; 27:841–844.

4 Biswas M, Ghosh S, Ghosh K, Chatterjee A, Dasgupta S, Ganguly P. Prevalence, types, clinical associations, and determinants of peripheral neuropathy in rheumatoid patients. Ann Indian Acad Neurol 2011; 14: 194–197.

5 Kerry R, Holt G, Stockley I. The foot in chronic rheumatoid arthritis: a continuing problem. Foot 1994; 4:201–203.

6 Borman P. Foot problems in a group of patients with rheumatoid arthritis: an unmet need for foot care. Open Rheumatol J 2012; 6:290–295.

7 Wakefield R, Gibbon W, Conaghan P, O'Connor P, McGonagle D, Pease C, *et al.* The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum 2000; 43:2762–2770.

8 Aletaha D, Neogi T, Silman A, Funovits J, Felson D, Bingham, C, *et al.* Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62:2569–2581.

9 Berker E, Dinçer N Chronic pain and rehabilitation. Agri 2005; 17:10–16.

10 Fransen J, Creemers MCW, Van Riel PLCM. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatol J 2004; 43:1252–1255

11 Waller R, Manuel P, Williamson L. The Swindon foot and ankle questionnaire: is a picture worth a thousand words? ISRN Rheumatol 2012; 2012:1–8.

12 Stanford Patient Education Research Center. Stanford HAQ 8-Item Disability Scale; 2015. Available at: *http://patienteducation.stanford.edu/research/haq8.html.* [Last accessed on 2015 Sep 20].

13 Barohn RJ. Muscle diseases. In: Wyngaarden JB, Smith LH, editors. *Cecil text of medicine.* Philadelphia: Saunders; 1982. P2013–P2043.

14 Rocha OMD, Batista ADAP, Maestá N, Burini RC, Laurindo IMM. Sarcopenia in rheumatoid cachexia: definition, mechanisms, clinical

consequences and potential therapies. Rev Bras Reumatol 2009; 49: 288–301.

15 Montagna P, Liguori R. The motor Tinel sign: a useful sign in entrapment neuropathy?. Muscle Nerve 2000; 23:976–978.

16 Chung T, Yen J, Ou T, Liu H, Tsai W. Prevalence of neuropathic pain in patients with rheumatoid arthritis. Formosan J Rheumatol 2009; 23:19–24.

17 Kim W, Kim H, Bluementhal F, Joynt R. Antidromic sensory nerve conduction studies of medial and lateral plantar nerves in normals. Electromyogr Clin Neurophysiol 1993; 33:289–294.

18 Buschbacher R, Prahlow N *Manual of nerve conduction studies*. New York, NY: Demos; 2006.

19 Preston D, Shapiro B. Artefacts and technical factors. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013.71–89.

20 Preston D, Shapiro B. Basic nerve conduction studies. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013.19–35.

21 Preston D, Shapiro B. Routine lower extremity nerve conduction. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013.115–124.

22 Preston D, Shapiro B. Tarsal tunnel syndrome. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013.365–372.

23 Preston D, Shapiro B. Basic overview of electromyography. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013. 125–128.

24 Preston D, Shapiro B. Anatomy for needle electromyography. In: Preston D, Shapiro B, editors. *Electromyography and neuromuscular disorders*. 3rd ed. Philadelphia: Elsevier; 2013. 174–190.

25 Kaplan P, Kernahan J. Tarsal tunnel syndrome: an electrodiagnostic and surgical correlation. J Bone Joint Surg 1981; 63:96–99.

26 Aprile I, Tonali P, Caliandro P, Pazzaglia C, Foschini M, Di Stasio E *et al.* Italian multicentre study of peroneal mononeuropathy: multiperspective follow-up. Neurol Sci 2009; 30:37–44.

27 Weiss L. Injury to peripheral nerves. In: Weiss L, Silver J, Weiss J, editors. *Easy EMG*. 1st ed. Edinburgh: Butterworth-Heinemann; 2004. 81–86.

28 Masakado Y, Kawakami M, Suzuki K, Abe L, Ota T, Kimura A. Clinical neurophysiology in the diagnosis of peroneal nerve palsy. Keio J Med 2008; 57:84–89.

29 Riente L, Delle Sedie A, Iagnocco A, Filippucci E, Meenagh G, Valesini G, *et al.* Ultrasound imaging for the rheumatologist V. ultrasonography of the ankle and foot. Clin Exp Rheumatol 2006; 24:493–498.

30 Naredo E, Collado P, Cruz A, Palop M, Cabero F, Richi P, *et al.* Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum 2007; 57:116–124

31 Brown A, Quinn M, Karim Z, Conaghan P, Peterfy C, Hensor E, *et al.* Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission. Arthritis Rheum 2006; 54:3761–3773.

32 Marhadour T, Saraux A. Rheumatoid arthritis assessment with ultrasonography. In: Thoirs K, editor. *Sonography*. Rijeka: InTech; 2012. ISBN: 978-953-307-947-9. Available at: *http://www.intechopen.com/books/sonography/rheumatoid-arthritis-assessment-with-ultrasonography*

33 Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, *et al.* Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005; 32:2485–2487.

34 Koenig R, Pedro M, Heinen C, Schmidt T, Richter H, Antoniadis G, *et al.* High-resolution ultrasonography in evaluating peripheral nerve entrapment and trauma. Neurosurg Focus 2009; 26:E13.

35 Wolfe AM. The epidemiology of rheumatoid arthritis: a review. I. Surveys. Bull Rheum Dis 1968; 19:518–523.

36 Kvien T, Uhlig T, Ødegård S, Heiberg M. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 2006; 1069:212–222.

37 Stucki G, Schönbächler J, Brühlmann P, Mariacher S, Stoll T, Michel B. Does a muscle strength index provide complementary information to traditional disease activity variables in patients with rheumatoid arthritis? J Rheumatol 1994; 21:2200–2205.

38 Stucki G, Bruhlmann P, Stucki S, Michel B. Isometric muscle strength is an indicator of self-reported physical functional disability in patients with rheumatoid arthritis. Rheumatology. 1998; 37:643–648.

39 Willer B. Effects of creatine supplementation on muscle weakness in patients with rheumatoid arthritis. Rheumatology 2000; 39:293–298.

40 Engvall I, Elkan A, Tengstrand B, Cederholm T, Brismar K, Hafström I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. Scand J Rehabil Med 2008; 37:321–328.

41 Chen Y, Chen H, Hsieh C, Hsieh T, Lan J, Chen D. A close association of body cell mass loss with disease activity and disability in Chinese patients with rheumatoid arthritis. Clinics 2011; 66:1217–1222.

42 Welsing P, Van Gestel A, Swinkels H, Kiemeney L, Van Riel P. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001; 44:2009–2017.

43 Boyd T, Bonner A, Thorne C, Boire G, Hitchon C, Haraoui B, *et al.* The relationship between function and disease activity as measured by the HAQ and DAS28 varies over time and by rheumatoid factor status in early inflammatory arthritis (EIA). Results from the CATCH Cohort. Open Rheumatol J 2013; 7:58–63.

44 Nunez-Cornejo Piquer C, Nunez-Cornejo Palomares C, Ivorra Cortes J, Grau E, Chalmeta Verdejo I, Molina Almela C, *et al.* AB0230 relationship between HAQ, DAS28 and radiological damage with functional capacity of the hand in rheumatoid arthritis. Ann Rheum Dis 2014; 73:879–880.

45 Bekkelund S, Torbergsen T, Omdal R, Husby G, Mellgren S. Nerve conduction studies in rheumatoid arthritis. Scand J Rheumatol 1996; 25:287–292.

46 Kadhim A, Abdul-Kareem A, Hamdan F. Peripheral neuropathy in rheumatoid arthritis: a clinical and neurophysiological study. Iraqi J Med Sci. 2003; 2:376–382.

47 Sulaiman M, Sulaiman S, Majdal H. Nerve conduction and electromyography in rheumatoid arthritis patients: a case–control study. Ann Coll Med Mosul 2012; 38:44–51.

48 Bekkelund S, Torbergsen T, Husby G, Mellgren S. Myopathy and neuropathy in rheumatoid arthritis. A quantitative controlled electromyographic study. J Rheumatol 1999; 26:2348–2351.

49 Abdullah Q, Rasool M, Qader T. Assessment of neurophysiologic changes and disease activity in patients with chronic rheumatoid arthritis. Jordan Med J 2013; 47:131–141.

50 Olney R. Neuropathies associated with connective tissue disease. Semin Neurol 1998; 18:63–72.

51 Nadkar M, Agarwal R, Samant R, Chhugani S, Idgunji S, Iyer S, *et al.* Neuropathy in rheumatoid arthritis. J Assoc Physicians India 2001; 49:217–220.

52 Khedr E, Herdan O, Khalifa H, Ali A, El Fetoh N, El-Hammady D, *et al.* Clinical and subclinical neuropsychiatric abnormalities in rheumatoid arthritis patients. Egypt Rheumatol Rehabil. 2015; 42:11–18.

53 Turesson C, Matteson E. Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol 2009; 21:35–40.

54 Aktekin L, Gözlükaya H, Bodur H, Borman P, Köz Ö. Peripheral neuropathy in rheumatoid arthritis patients; an electroneurophysiological study. Turk J Rheumatol 2009; 24:62–64.

55 Ramos-Remus C, Duran-Barragan S, Castillo-Ortiz J. Beyond the joints. Clin Rheumatol 2011; 31:1–12.

56 Rubin D, Daube J. Nerve conduction studies. Aminoff's Electrodiagnosis in Clinical Neurology. 6th ed. Philadelphia: Saunders/ Elsevier; 2012. p. 289-326.

57 Herbison GJ, Teng C, Martin JH, Ditunno JF Jr. Carpal tunnel syndrome in rheumatoid arthritis. Am J Phys Med 1973; 52–68.

58 Fleming A, Dodman S, Crown J, Corbett M. Extra-articular features in early rheumatoid arthritis. BMJ 1976; 1:1241–1243.

59 Lanzillo B, Pappone N, Crisci C, Di Girolamo C, Massini R, Caruso G. Subclinical peripheral nerve involvement in patients with rheumatoid arthritis. Arthritis Rheum 1998; 41:1196–1202.

60 Bayrak A, Durmus D, Durmaz Y, Demir İ, Canturk F, Onar M. Electrophysiological assessment of polyneuropathic involvement in rheumatoid arthritis: relationships among demographic, clinical and laboratory findings. Neurol Res 2010; 32:711–714.

61 Sim M, Kim D, Yoon J, Park D, Kim Y. Assessment of peripheral neuropathy in patients with rheumatoid arthritis who complain of neurologic symptoms. Ann Rehabil Med 2014; 38:249–255.

62 Oh S. Neuropathies of the foot. Clin Neurophysiol 2007; 118:954–980.

63 Baylan S, Paik S, Barnert A, Ko K, Yu J, Persellin R. Prevalence of the tarsal tunnel syndrome in rheumatoid arthritis. Rheumatology 1981; 20:148–150.

64 Helliwell P. Clinical features of the foot in rheumatoid arthritis. In: Helliwell P, editor. *The foot and ankle in rheumatoid arthritis*. 1st ed. Edinburgh: Churchill Livingstone/Elsevier; 2007. p. 57–74.

65 Nakano K. Entrapment neuropathy from Baker's cyst. JAMA 1978; 239:135b-135b.

66 Katirji B, Peroneal neuropathy. Neurol Clin 1990; 17:567–591.

67 Sourkes M, Stewart J. Common peroneal neuropathy: a study of selective motor and sensory involvement. Neurology 1991; 41:1029–1029.

68 Soliman S, Korah T, Hammoda G, Mousa W. Significance of serum levels of angiopoietin-2 and its relationship to Doppler ultrasonographic findings in rheumatoid arthritis patients. Egypt Rheumatol 2014; 36: 15–20.

69 Naredo E, Möller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to antitumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum 2008; 58:2248–2256.

70 Oh SJ, Sarala PK, Kuba T, Elmore RS. Tarsal tunnel syndrome: electrophysiological study. Ann Neurol 1979; 5:327–330.

71 Oh SJ, Kim HS, Ahmad BK. The near-nerve sensory nerve conduction in tarsal tunnel syndrome. J Neurol Neurosurg Psychiatry 1985; 48: 999–1003.

72 Galardi G, Amadio S, Maderna L, Meraviglia M, Brunati L, Conte G, *et al.* Electrophysiologic studies in tarsal tunnel syndrome. Am J Phys Med Rehabil 1994; 73:193–198.

73 Mondelli M, Giannini F, Reale F. Clinical and electrophysiological findings and follow-up in tarsal tunnel syndrome. Electroencephalogr Clin Neurophysiol 1998; 109:418–425.

74 Mondelli M, Morana P, Padua L. An electrophysiological severity scale in tarsal tunnel syndrome. Acta Neurol Scand 2004; 109:284–289.

75 Patel AT, Gaines K, Malamut R, Park TA, Toro DR, Holland N, *et al.* Usefulness of electrodiagnostic techniques in the evaluation of suspected tarsal tunnel syndrome: an evidence based review. Muscle Nerve 2005; 32:236–240.