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Ankle involvement in rheumatoid arthritis – a comparison of inflammatory signs on musculoskeletal ultrasound and magnetic resonance imaging

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Abstract

Aim: To evaluate the frequency of tibiotalar and subtalar joints together with extensor, flexor and peroneal tendons inflammatory lesions in rheumatoid arthritis (RA) patients by using ultrasound (US) and magnetic resonance imaging (MRI). **Material and methods**. Fifty RA patients and 25 healthy subjects were prospectively included. All patients and controls underwent clinical examination (to screen for swollen and/or tender ankles) and ankle US and MRI (to screen for synovial hypertrophy – SH, tenosynovitis and power Doppler – PD signals). The imaging tests were compared using overall agreement, positive agreement, Cohen's κ, sensitivity, specificity and positive likelihood ratio. **Results**. The subtalar joint had the highest frequency of US-detected SH (30%), as well as positive PD signals (10%). Regarding US joint effusion, the tibiotalar joint recorded the highest frequency (44%). The most frequent US tenosynovitis was detected in the tibialis posterior tendon (40%). Compared to MRI, US evaluation of tibiotalar joints had very good agreement and large effect on detection probability for both SH and effusion (kappa 0.84, positive likelihood ratio 21.1). Compared to MRI, the sensitivity and specificity for US joint involvement ranged between 72.0-88.5% and 82.4-95.8%, and for tenosynovitis were 33.3-78.6% and 85.2-100%, respectively. Compared to asymptomatic RA patients (n=25), those with at least one symptomatic ankle (n=25) had significantly higher frequencies of both SH and effusion in all the evaluated structures. **Conclusion:** US has high sensitivity and specificity in detecting RA inflammatory lesions in the ankle and rearfoot, in very good agreement with MRI. The high frequency of ankle inflammatory lesions in RA should result in increased interest in the imaging evaluation of these structures.

Keywords: rheumatoid arthritis; musculoskeletal ultrasound; magnetic resonance imaging; synovitis; tenosynovitis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects synovial joints, causing irreversible joint deformities which lead to important disability. Clinical examination for synovitis detection is an important tool in the diagnosis and evaluation of RA, but it has low accuracy and reproducibility [1]. Radiological examination reveals late bone destructive changes without being able to evaluate soft parts that can be affected from the onset of the disease [2]. New imaging techniques, musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI), can identify early articular and peri-articular inflammatory lesions, playing an important role in diagnosis, therapeutic decisions and monitoring of the disease [3-6].

The ankle and foot are affected by RA in more than 90% of patients during the disease course [7]: 20% of pa-

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tients have structural changes from disease onset, while 50% start displaying these changes in the first 6 years of illness [8]. Clinical ankle examination has low accuracy and it is influenced by many local factors (e.g. adjacent anatomical structures, deformities, obesity and venous insufficiency). In current practice, MRI is rarely used because of high costs, limited accessibility, motion artefacts and exposure to contrast agents. The superiority of US and MRI to clinical examination in early detection of inflammatory synovial lesions has been proved by numerous studies, especially in the hands [9,10]. Regarding the ankles, the literature is scarce and the few articles which research this area have focused especially on the forefoot [11,12]. However, despite the destructive potential of RA joint involvement, the ankle remains an anatomical region neglected in current practice. In particular, the ankle is not included in composite RA activity scores and there is little data from studies on ankle and rear-foot imaging, despite poor clinical examination [13-19].

Therefore, this study aims to evaluate the frequency of ankle and rear-foot inflammatory lesions (synovitis and tenosynovitis) in RA patients and to compare the US and MRI (as a reference standard) findings.

Materials and methods

Patients selection

In this prospective study, we evaluated 50 patients diagnosed with RA (fulfilling the 2010 ACR/EULAR criteria [20]) and 25 healthy controls subjects with no current or history of joint disease. RA patients were recruited in 2018 in random order of presentation from the outpatient clinic. All patients and controls underwent clinical examination, laboratory tests, US and MRI evaluation (contrast MRI for RA patients and native MRI for controls). Exclusion criteria included age below 18 years, severe deformity of ankle joints, ankle surgery/trauma, MRI contraindications, local complex regional pain syndrome, fibromyalgia, pregnancy, glucocorticoids (pulse-therapy, intramuscular, intra-articular injections) in the month prior to study inclusion. Oral doses of glucocorticoids of ≤10 mg prednisone equivalent which were stable in the month prior to study inclusion were allowed. All patients and healthy controls gave written informed consent prior to enrolment in the study. The study was approved by the local Ethics Committee.

Clinical examination and laboratory data

All patients and control subjects were clinically evaluated by the same rheumatologist, blinded to laboratory and imaging evaluations. The clinical examination of the ankles was made bilaterally and consisted of inspection, palpation and active movement of each compartment from ankle and subtalar region, in order to detect signs of inflammation (pain and swelling). Additionally, the rheumatologist noted concomitant local pathology: hallux valgus, pes planus, chronic venous insufficiency. Current conditions that could influence ankle symptoms (i.e. diabetes mellitus, chronic venous insufficiency, obesity and exclusion criteria) were retrieved from the patient's medical history. Laboratory data included rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).

US examination

The US scans were performed and interpreted by a single rheumatologist with more than 7 years of experience, on the same day with clinical examination and blinded to clinical and imaging results, using the EULAR ankle technique [21]. An Esaote MyLabTwice machine, equipped with a 12-18 MHz linear transducer was used. Both ankles were scanned. Tibiotalar joints (TTJ) with their anterior and posterior recesses and subtalar joints (STJ) from medial, lateral and posterior aspects were assessed. The following tendons were examined: tibialis anterior (TA), extensor hallucis longus (EHL), extensor digitorum longus (EDL), tibialis posterior (TP), flexor digitorum longus (FDL), flexor hallucis longus (FHL), peroneus longus (PL) and brevis (PB). The US examination included initial grey scale (GS), followed by power Doppler (PD) evaluation. Power Doppler settings were constant (gain just below noise level, 750 Hz pulse repetition frequency, 8-10 MHz Doppler frequency, low wall filter). The following pathologic findings were recorded: synovial hypertrophy (SH) and effusion at joint/tendon level. Their definitions and interpretation were made according to OMERACT recommendations [22]. For quantifying these pathologic findings, the following semi-quantitative scales (0-3) were used: for joint SH, the initial score developed by Szkudlarek et al [23,24], taking into account the latest EULAR-OMERACT recommendations [25], which were verified on large joints. For joints evaluated from multiple windows, the highest grade of SH was recorded. Joint effusion was quantified with a dichotomous score (present/absent). For tenosynovitis quantification, we applied the OMERACT recommended score [26].

MRI

A trained radiologist performed contrast MRI in RA patients and native MRI in controls (for ethical reasons), in the same day/ the next 2 days for each patient. The involved ankle was scanned in patients with unilateral symptomatic ankle. In RA patients with bilateral symptomatic/ asymptomatic ankles and also in healthy controls, the right ankle and rearfoot were evaluated. MRI was performed with a 1.5 Tesla General Electric Optima 450 WGEM machine, using a high definition dedicated

8-channel transmission antenna, on patients positioned in dorsal decubitus with their examined ankle in a neutral position. The examination protocol included: a) native acquisition proton-density-weighted fast spin echo (FSE) in axial, coronal and sagittal planes, T2-weighted FSE in coronal plane andT1-weighted FSE in sagittal plane with slice thickness of 4 mm, field of view (FOV) of 19 cm and matrix of 320 x 224 mm; b) acquisition of pre-contrast 3D T1-weighted spoiled gradient recalled (SPGR; liver acquisition with volume acceleration sequence - LAVA) in axial plane with slice thickness of 2 mm and FOV of 19 cm and matrix of 228 x 224 mm; two post-contrast acquisitions: and early 3D T1-weighted SPGR (LAVA) in axial plane with slice thickness of 2 mm and a late T1-weighted SPGR (LAVA) in a sagittal plane with a slice thickness of 3 mm. Contrast was administered intravenously (0.1 mmols of gadolinium-diethylenetriamine penta-acetic acid per kilogram of body weight) only in RA patients. For this subgroup, SH and effusion were evaluated separately for both joints (TTJ, STJ with their anterior and posterior recesses) and tendons (anterior, lateral, medial and posterior ankle compartments). These inflammatory lesions were defined according to OMERACT recommendations [27]. Grading of synovitis was done using the RAMRIS semi-quantitative score [28]. Tenosynovitis was graded using a separate semi-quantitative method [29].

Table I. General characteristics of rheumatoid arthritis patients (n=50)

Age (years)	**55(17)**
Women (%)	42(84)
Disease duration (years)	6(11)
Ankle symptoms (%)	25(50)
Rheumatoid factor positive (%)	34(68)
ACPA positive (%)	40(80)
NSAIDs (%)	5(10)
GC (%)	10(20)
GC dose (mg/day PE)	10(5)
MTX (%)	20(40)
MTX dose (mg/week)	10(10)
> 1 csDMARDs (%)	7(14)
tsDMARDs (%)	1(2)
bDMARDs (%)	17(34)
Diabetes mellitus (%)	7(14)
Hallux valgus (%)	7(14)
Obesity (%)	6(12)
CVI-LL (%)	11(22)
Pes planus (%)	3(6)

Continuous variables are expressed as "median (interquartile range)" and categorical variables are expressed as "number (percentage of group)". ACPA – anti-citrullinated protein antibodies; b/cs/tsDMARD – biological or conventional synthetic or targeted synthetic disease-modifying anti-rheumatic drug; CVI-LL – chronic venous insufficiency of lower limbs; GC – glucocorticoids; PE – prednisone equivalent; MTX – methotrexate

Statistics

Nominal variables are reported as "absolute frequency (percent of subgroup)". All recorded continuous variables were non-normally distributed and were reported as "median (inter-quartile range)". Differences between dichotomous groups were evaluated using Mann Whitney U and χ^2 tests. US's performance compared to MRI was evaluated with: overall agreement (OA), positive agreement (PA), Cohen's κ (kappa; strength of agreement: <0.2 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and >0.80 very good [30]); sensitivity, specificity and positive likelihood ratio (PLR; effect on increasing probability of involvement detection: PLR>10 large, PLR=5-10 moderate, PLR<5 small [31]). To compare ultrasound to MRI regarding SH/tenosynovitis grading, the cross-tabulation was reduced to a two-by-two table by grouping "absent-minimal" (grade 1 SH being difficult to appreciate as pathological) and "moderate-severe" (grade 2 and 3). The statistical tests were considered significant if $p<0.05$ and were done with IBM SPSS Statistics version 22.0 for Windows (Armonk, NY, IBM Corp.).

Results

General characteristics

The study included 50 RA patients and 25 controls. Demographic and laboratory data of RA patients are detailed in Table I.

Frequency of US inflammatory lesions in RA

STJ had the highest frequency of US-detected SH (30% versus 28% in TTJs), as well as PD signals (10% versus 6% in TTJs). Regarding joint effusion, TTJ recorded a higher frequency (44% versus 38 % in STJ). The most frequent tenosynovitis was detected in TP tendon sheath (40%), with 38% SH and 34% positive PD signal. Most frequently, US detected effusion in the TP (28%). The posterior recess of STJ proved to be the most reliable for SH and effusion detection. The lateral STJ window offered the best view for PD signal detection (Table II, Table III).

Frequency of MRI inflammatory lesions in RA

Table II presents the summary of lesions detected on MRI, which proved to be superior to US in joint SH detection. In MRI, both TTJ and STJ recorded the same frequency of involvement (32%); in the case of TTJ, the difference between the two imaging methods being higher. MRI was also superior to US in detecting joint effusion (50% in TTJ and 42% in STJ). Regarding tenosynovitis,

MRI remained superior to US, recording TP tenosynovitis in 46% of RA patients. Similar to US, MRI detected effusion most frequently in TTJ (50%) and TP (26%).

US compared to MRI in RA

Compared to MRI, US evaluation of TTJs had very good agreement for both SH and effusion (fig 1), including SH grading. However, STJs evaluation produced moderate to good agreement and moderately increased the chance of detection of both SH and effusion. In tendons, the highest agreement compared to MRI was achieved for overall US involvement (SH and effusion) of EDL (Table IV), while the lowest performance of US was recorded for overall involvement of TA and FHL.

Symptomatic versus asymptomatic ankles

Compared to asymptomatic RA patients (n=25), those with at least one symptomatic ankle (n=25) had significantly lower median age and significantly higher frequencies of both SH and effusion in all the evaluated structures. PD signal was more frequently detected in symptomatic patients, both in joints (24% versus 0%, p=0.009) and tendons (84% versus 12%, p<0.001) (Table IV). These two groups did not differ significantly regarding the frequency of positive RF, ACPA, treatment regime and recorded comorbidity (p>0.1). In the asymptomatic RA subgroup, there were 10 (20%) patients with normal US, 11 (22%) with normal MRI and 6 (12%) with normal aspect in both imaging techniques.

US compared to MRI in controls

The control group (n=25) had a median age of 53 years and included 21 women (84%). Unlike US, native MRI cannot differentiate effusion from SH, detecting only distension of joint capsules and tendon sheaths. In the control group US revealed effusion in 5 (20.0%) TTJs and in 9 (36.0%) STJs, with very good agreement with MRI (kappa = 0.82 and 0.83 respectively). Regarding tendon involvement, US also detected only intra-tendon sheath effusion in the TP (5 cases), FHL (5 cases) and FDL (4 cases) tendons, with good and very good agreement with MRI (κ>0.63, PLR>11). US detected no ankle/tendon PD signals.

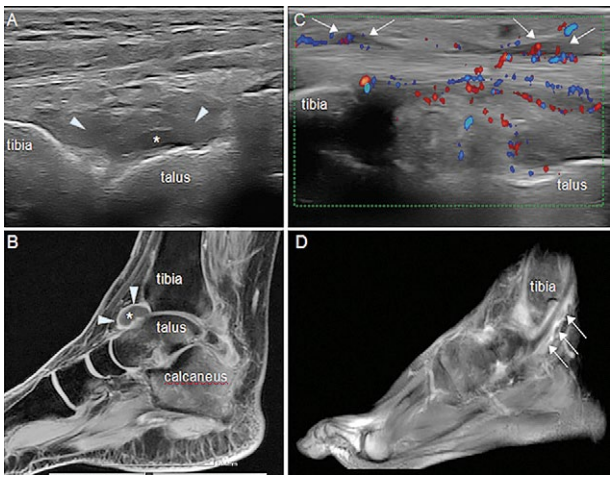

Fig 1. Longitudinal US image (A) and sagittal T1 weighted post-gadolinium 3D LAVA MRI (B) at anterior recess of tibiotalar joint reveal synovial hypertrophy (arrow heads) and joint effusion (*) in an RA patient. Longitudinal US image (C) and sagittal T1 weighted fat saturated post-gadolinium MRI image (D) of tibialis posterior tendon reveal tenosynovitis (arrows) with synovial proliferation and peri- and intra-tendineous PD signals in an RA patient.

Table II. Ultrasound–MRI comparison on RA ankle joint involvement (n=50 patients)

	US (n)	MRI (n)	OA (%)	PA (%)	κ	Se (%)	Sp (%)	PLR
overall (effusion and SH)								
TTJ	24	26	92	95.8	0.84*	88.5	95.8	21.1
STJ	22	25	78	81.8	0.56*	72.0	84.0	4.5
any	29	33	80	89.7	0.58*	78.8	82.4	4.5
effusion presence								
TTJ	22	25	90	95.5	0.80*	84.0	96.0	21.0
STJ	19	21	80	78.9	0.58*	71.4	86.2	5.2
SH presence								
TTJ	14	16	92	92.9	0.81*	81.2	97.1	28.0
STJ	15	16	86	80.0	0.67*	75.0	91.2	8.5
grade 2 and 3 SH								
TTJ	7	5	96	71.4	0.81*	100	95.6	22.7
STJ	9	2	86	22.2	0.32*	100	85.4	6.8

κ's significance: * p<0.007; US – ultrasound; MRI – magnetic resonance imaging; OA – overall agreement; PA – positive agreement; PLR – positive likelihood ratio; RA – rheumatoid arthritis; Se – sensitivity; SH – synovial hypertrophy; Sp – specificity; STJ – subtalar joint; TTJ – tibiotalar joint.

Table III. The frequency of positive PD signals in RA patients (n=50)

joint cases	TTJ	STJ	pSTJ	lSTJ	mSTJ	any			
	3(6)	5(10)	0	4(8)	1(2)	6(12)			
tendon cases	TA	EHL	EDL	PL	PB	TP	FDL	FHL	any
	3(6)	2(4)	4(8)	10(20)	7(14)	17(34)	8(16)	4(8)	24(48)

The results are expressed as number (%). EDL – extensor digitorum longus; EHL – extensor hallucis longus; FDL – flexor digitorum longus; FHL – flexor hallucis longus; l – lateral; m – medial; p – posterior; PB – peroneus brevis; PL – peroneus longus; RA – rheumatoid arthritis; TA – tibialis anterior; TP – tibialis posterior; STJ – subtalar joint; TTJ – tibiotalar joint.

Table IV. Ultrasound-MRI comparison on ankle tendon involvement in RA (n=50 patients)

		US(n)	**MRI(n)**	**OA(%)**	**PA(%)**	**κ**	**Se(%)**	**Sp(%)**	**PLR**
overall	TA	3	9	90	100	0.45*	33.3	100	-
	EHL	2	5	94	100	0.55*	40.0	100	-
	EDL	7	8	94	85.7	0.80*	75.0	97.6	31.3
	PL	14	14	88	78.6	0.70*	78.6	91.7	9.5
	PB	11	11	88	72.7	0.65*	72.7	92.3	9.4
	TP	20	23	78	80.0	0.55*	69.6	85.2	4.7
	FDL	12	15	76	83.3	0.65*	66.7	94.3	11.7
	FHL	8	19	78	100	0.47*	42.1	100	-
	Any	29	28	86	86.2	0.72*	89.3	81.8	4.9
effusion presence	TA	3	4	98	100	0.85*	75.0	100	-
	EHL	1	0	-	-	-	-	-	-
	EDL	6	4	92	50.0	0.56*	75.0	93.5	11.5
	PL	9	9	80	44.4	0.32*	44.4	87.8	3.6
	PB	6	3	86	16.7	0.16#	33.3	89.4	3.1
	TP	14	13	82	64.3	0.54*	69.2	86.5	5.1
	FDL	8	4	88	37.5	0.44*	75.0	89.1	6.9
	FHL	7	14	86	100	0.59*	50.0	100	-
SH presence	TA	3	8	90	100	0.50*	37.5	100	-
	EHL	2	5	94	100	0.55*	40.0	100	-
	EDL	5	6	94	80.0	0.69*	66.7	97.7	29.0
	PL	11	11	96	90.9	0.88*	90.9	97.4	35.0
	PB	9	11	88	77.8	0.63*	63.6	94.9	12.5
	TP	19	20	82	78.9	0.62*	75.0	86.7	5.6
	FDL	9	13	84	77.8	0.54*	53.8	94.6	10.0
	FHL	5	11	88	100	0.57*	45.5	100	-
grade 2 and 3 SH	TA	3	5	96	100	0.73*	60.0	100	-
	EHL	1	0	-	-	-	-	-	-
	EDL	5	4	94	60.0	0.63*	75.0	95.7	17.4
	PL	7	10	86	71.4	0.51*	50.0	95.0	10.0
	PB	3	2	94	33.3	0.37*	50.0	95.8	11.9
	TP	14	14	96	92.9	0.90*	92.9	97.2	33.2
	FDL	4	5	90	50.0	0.39*	40.0	95.6	9.1
	FHL	5	17	76	100	0.36*	29.4	100	-

κ's significance: * $p \leq 0.023$; # non-significant; - incalculable (division by 0 or all ratings are the same for MSUS and/or MRI); US – ultra-sound; MRI – magnetic resonance imaging fndings; OA – overall agreement; PA – positive agreement; PLR – positive likelihood ratio; RA – rheumatoid arthritis; Se – sensitivity; SH – synovial hypertrophy; Sp – specificity; tendons: EDL – extensor digitorum longus; EHL – extensor hallucis longus; FDL – flexor digitorum longus; FHL – flexor hallucis longus; PB – peroneus brevis; PL – peroneus longus; TA – tibialis anterior; TP – tibialis posterior.

Discussions

Taking into account that there is scarce literature on the frequency of inflammatory lesions in the ankles of RA patients, our study brings important information to this subject. The results have revealed a very good agreement (both in joints and tendons) between US and MRI findings.

Concerning the frequency of inflammatory lesions, our study found similar data to previous studies performed on subgroups of patients (symptomatic or asymptomatic ankles) [13,19,32,33]. In the only study that evaluated ankle using US regardless of the presence of symptoms, Alsawaidi et al [34] reported higher frequency of TTJ and lower frequency of TP and FDL involvement.

The literature contains few reports of US comparison to MRI in the evaluation of ankle involvement in RA patients. In a study published in 1996, Lehtinen et al [15] reported high concordance between US and high field MRI findings but their results are difficult to be compared with our results due to the technological differences of imaging machines used and by differences in study design. Wakefield et al [19] reported the same pattern of US performance in detecting ankle joint and tendon involvement, generally with lower sensitivity and specificity of TTJ and tendon involvement compared to our observations. Taken together, these two studies and our results seem to confirm the overall good performance of US compared to MRI in evaluation RA involvement of ankle structures.

Concerning the agreement between US and MRI, Premkumar et al [35] reported sensitivities and specificities above 80% for US detection of TP and FDL involvement compared to MRI. We report slightly lower sensitivities and higher specificities of US compared to MRI for the detection of anomalies in these tendons, in a homogenous and larger group of RA patients. However, the results of this study are not directly comparable to our observations, since the authors evaluated patients with different forms of spondyloarthritis, which are known to generate important structural abnormalities of tendons [36]. Scheel et al [37] found low agreement of US with MRI on overall involvement of TTJs (57% compared to 92% in our study), STJs (57% compared to 78% in our study) and extensor tendons (36% compared to 90% in our study) and good agreement on overall involvement of flexors (86% compared to 82% in our study) and peroneus tenosynovitis (71% compared to 88% in our study).

Unlike previous studies, for a more accurate comparison between US and MRI, we differentiated by US effusion from SH in joints and tendon sheaths. This allowed us to understand the low agreements recorded in some structures, regarding the overall assessment. For example, in the case of TA, EHL and FHL, the low agreement is caused by low sensitivity of US to detect what MRI identify as grade 1 synovial hypertrophy. More so, joint by joint analysis (PA=100% in all three tendons) underlines that all the pathologic findings detected by US were confirmed by MRI. In addition, the latter detected more minimal proliferation in the tendon sheath, possibly overestimating true pathological lesions. We included PD signals in the US examination, increasing the US specificity for SH detection. Also, special attention was paid to the posterior foot (posterior recess of TTJ and STJ), which was not included in the cited articles.

We note the low incidence of PD in the ankle joints, which can be explained by the low sensitivity of PD for large joints and deep anatomic areas. The same low PD frequency in TTJ was also noted by other authors [13,34,38,39], who proposed to further scan the lateral and medial aspects of TTJ's anterior recess in order to increase PD sensitivity. Regarding STJ, PD signals were detected only in the medial and lateral recesses.

By including healthy controls in our study, we aimed to identify truly pathological findings. The presence of effusion in ankle joints/ tendon sheaths in normal individuals draws attention to other possible causes, not necessarily inflammatory.

The interpretation of our results needs to be performed in light of several study limitations: we did not perform an inter- and intra-observer agreement; conventional radiography was not done and neither bone damage evaluation; not all MRI scans were in the same day as clinical and US evaluations. For ethical reasons, controls were evaluated by native MRI, in order to mitigate potential risks of contrast substance.

In **conclusion** US has high sensitivity and specificity in detecting RA inflammatory lesions in the ankle and rearfoot, generally in very good agreement with MRI. For the detection of PD signals, a more elaborate examination of the ankle may be necessary, as well as a standardized ankle and rearfoot evaluation protocol. Although ankles are not routinely evaluated in clinical practice despite the destructive potential and implicitly the functional deficit of RA, the high frequency of inflammatory lesions at this level should result in increased interest in the imaging evaluation of these structures.

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