To what extent is foot pain related to biomechanical changes and ultrasound-detected abnormalities in rheumatoid arthritis?

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Abstract

Objective

To investigate the presence of biomechanical abnormalities and ultrasound (US)-detected inflammation and damage in low disease or remission status rheumatoid arthritis (RA) patients with foot complaints.

Methods

We recruited 136 subjects with foot complaints. Sixty-two were biologic disease-modifying antirheumatic drug-treated RA patients presenting Disease Activity Score-determined remission or low disease activity while the remaining 74 were gender matched controls without rheumatic or musculoskeletal disorders. Both groups underwent a comprehensive podiatric, biomechanical and B-mode and Doppler US assessment of the feet.

Results

Most RA patients and controls were female (77.4% and 83.8%, respectively). There was no statistical difference in the proportion of obese subjects in either group (p=0.792). Inappropriate shoes were used by 50.0% of RA patients and 33.8% of controls (p=0.080). Talalgia, particularly heel pain, was more frequent in the control group, with associated talalgia and metatarsalgia being more prevalent in the RA group (p<0.05). The RA patient group was also more likely to present greater foot deformity, more limited joint movement and biomechanical abnormalities than the controls (p<0.05). US inflammatory and structural changes were significantly more frequent in RA patients than in controls (p<0.05). US structural involvement was significantly associated with limited joint mobility and pathologic biomechanical tests only in RA patients (p<0.05).

Conclusion

RA foot complaints seemed to be linked to US-detected RA involvement and biomechanical abnormalities. Podiatric and US assessments can be useful to help the clinician to optimise the management of RA patients in remission/low disease activity with foot complaints.

Key words

rheumatoid arthritis, foot, ankle, ultrasound, podiatry

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Introduction

A high prevalence of foot pain (70–90%) has been widely described in both early and late stages of rheumatoid arthritis (RA) (1-4). Foot inflammation in RA usually starts in the metatarsophalangeal (MTP) joints, often extends to other joints and tendons and progressively causes erosions, articular cartilage damage and luxation of the toe joints and a collapse of the transverse arch of the foot with consequent pain, deformities and functional impairment (5, 6). On the other hand, foot complaints are very common in the general population, often meaning patients suffer functional incapacity and diminished life (7).

Various indices that combine clinical and laboratory parameters are used to evaluate RA disease activity upon which a therapeutic decision is based. The disease activity score for 28 joints (DAS28) is possibly the most commonly used in clinical practice (8) but does not, however, include a direct assessment of the foot joints. In everyday clinical practice, it is not uncommon for successfully-treated RA patients in remission under the DAS28 criterion to present foot complaints (9, 10). Establishing whether this pain is inflammatory, RA disease-related or is down to other biomechanical factors, is not easy due to the complexity of this anatomic area. Such patients may run the risk of joint damage progression owing to disease activity under diagnosis.

Over the last decade, musculoskeletal (MS) ultrasound (US) has proved increasingly invaluable in the assessment of disease activity in RA patients (11-14). More specifically, a number of recent studies have demonstrated US ability to detect B-mode synovitis and synovial Doppler activity in a high percentage of RA patients in clinical remission (15-17). In addition, MSUS has proven validity and added value over conventional radiography in detecting structural damage in RA target joints (18, 19). However, a few studies have focused on US assessment of foot involvement in RA (20-23).

We hypothesise that RA foot involvement may be underestimate in clinical practice in terms of biomechanical abnormalities and residual inflammation which may benefit from additional podiatric and/or drug therapy. Therefore, the aim of this cross-sectional study was to investigate the presence of biomechanical abnormalities and US-detected inflammation and damage in low disease or remission status RA patients as compared to healthy subjects, both with foot complaints.

Methods

Study population

Sixty-two patients diagnosed with RA under the American College of Rheumatology 1987 criteria (24) were consecutively recruited at the Department of Rheumatology of the Hospital GU Gregorio Marañón (Madrid, Spain). The inclusion criteria were: (i) being aged 18 years or over, (ii) having been RA diagnosed at least two years prior to the study start date, (iii) being under treatment with a biologic disease-modifying antirheumatic drug (bDMARD) for at least 6 months, (iv) being in clinical remission (DAS28<2.6) or low disease activity (DAS28<3.2), (v) having had a foot complaint for at least three consecutive months, (vi) able to participate in the study. The exclusion criteria were: i) previous foot surgery or injury, ii) concomitant autoimmune or inflammatory disease, iii) diabetes mellitus, iv) neurological diseases, and v) congenital deformities. Seventy-four gender matched controls were included in the study with the following criteria: (i) being aged 18 years or over, (ii) having had a foot complaint for at least three consecutive months, (iii) not having a diagnosis of rheumatic or musculoskeletal disorder, (iv) able to participate in the study and that they met the same exclusion criteria as RA patients. All RA patients and non-RA controls signed the informed consent. This study was approved by the Medical Ethics Committee of the Hospital GU Gregorio Marañón (Madrid, Spain) and was conducted in full accordance with the Declaration of Helsinki (1964).

Clinical and laboratory assessment

Demographic and clinical characteristics of the RA patients were obtained from the electronic medical database of our department (MixeTB™ HGUGM): dis-

ease duration, current conventional synthetic (CS) DMARDs and bDMARDs, concomitant corticosteroids and the presence of radiographic erosions were recorded at recruitment. Disease activity was measured according to the DAS28 scale, using the erytrocyte sedimentation rate (ESR). Rheumatoid factor (RF) (nephelometry; >20 IU), and anti-citrullinated peptide antibodies (ACPAs) (second generation commercial enzyme-linked immunosorbent assay (Immunoscan RA); Euro-Diagnostica, Malmö, Sweden; >25 IU) were also obtained at recruitment. Nutritional status was classified as normal weight, body mass index (BMI) <25), overweight (25 <BMI <30) and obesity (BMI ≥30).

Podiatric assessment

All RA patients and controls underwent a comprehensive podiatric examination by a doctor of podiatric medicine (DPM) highly experienced (*i.e.* >20 years) in the pathology and biomechanics of the foot. Data on the appropriateness of footwear including the relation between the length of the shoe and the length of the foot under load, the use of foot orthoses or therapeutic footwear, and whether patients had special foot care were also collected. Foot pain was quantified by a 0 (no pain) to 10 (severe pain) score using a patient visual analog scale (VAS) (24, 25). Foot pain was classified as inflammatory (*i.e.* exacerbated by rest), mechanical (*i.e.* produced by movements), mixed or neuropathic (*i.e.* pain associated with numbness and tingling) according to how the patient described it.

All anatomical areas of the feet were examined by palpation. Pain on palpation was anatomically classified as follows: ankle pain, *i.e.* tibiotalar joint; talsalgia, *i.e.* subtalar, Chopart and Lisfranc joints; metatalsalgia, *i.e.* MTP and interphalangeal joints; and talalgia, *i.e.* heel or fascial pain. The areas of plantar and dorsal hyperkeratosis were recorded. Toe deformities, *i.e.* hallux valgus, Taylor's bunion, hammer and claw toe, were also recorded.

The biomechanical investigation consisted of the following:

1. mobility of the ankle, (26) subtalar and first MTP joints (27);
2. the calcaneus relaxed position test (RCSP) (28);
3. the standing heel-rise test (SHRT) (29);
4. the Jack test or Hubscher maneuver (30);
5. the foot postural index (FPI) (27);
6. footprint evaluation on podoscope (31).

Dorsiflexion of the ankle was measured with the knee flexed and the heel in contact with the ground using a goniometer aligned with the floor (stable arm). Dorsiflexion of the 1st MTP joint was also measured using a goniometer with the stable arm in the medial metatarsal region and the mobile arm in the medial region of the first toe. The patient lies prone on a flat examination table and the knee is placed in the frontal plane. The examiner then passively moves the subtalar joint into its end range of inversion and eversion motion. The average range of motion of the subtalar joint is 30 degrees: 20 degrees of inversion motion plus 10 degrees of eversion motion (27). Abnormal mobility was considered as <25°-30° for the ankle; <5°-10° eversion and <20°-10° inversion for the subtalar joint; and <30° for the 1st MTP (26, 27, 32, 33).

The RCSP determine the calcaneal stance position, *i.e.* varus or valgus, by measuring the angle between the calcaneal bisection and the floor plane (<5° of valgus was considered normal).

The SHRT consists of placing the patient firstly on tiptoe with both feet (double) and then on each foot (single). Failure to correct the heel varus position while performing the lift maneuver indicates either presence of bone synostosis, subtalar joint involvement, tibialis posterior lesions or any such combination. The test also helps to determine a rigid foot from a flexible flatfoot.

The Jack test is a forced dorsiflexion of the big toe. This test serves not only to distinguish a flexible foot from a rigid flat foot, but also to diagnose posterior tibialis dysfunction. To perform this test patients are asked firstly to march on the spot for several seconds to ensure even load distribution. Following that, a forced dorsiflexion of the big toe is performed; normally, this maneuver produces an increase of the longitudinal medial arch, an external rotation of the tibia and a calcaneus varus position. This test allows us to differentiate a flexible flatfoot from a rigid flatfoot as well as enabling us to detect posterior tibialis dysfunction.

The FPI is performed to identify foot pronation or supination. The aim is to assess the overall position of the foot in relaxed standing position using 6 clinical criteria, total score from -12 to + 12. Scores range from -2 to 2 and are graded as follows: -2, if there are clear signs of supination; 0, if it is neutral; +2, if there are clear signs of pronation. Both supination and pronation are pathological (32, 33).

The footprint was analysed using an ultralight Podoscope 50 cm x 50 cm (Herbitas, Foios, Valencia, Spain). While the patients are standing on the glass of the podoscope, the footprint is reflected onto the mirror. Footprint normality is defined as straight longitudinal axis, support of the toes and an isthmus width of 1/3 of the forefoot.

US assessment

All RA patients and controls underwent a comprehensive US assessment which was performed by a podiatrist experienced in musculoskeletal US (*i.e.* >5 years) who was unaware of the group (RA versus control) clinical and laboratory data. This assessment consisted of a systematic longitudinal and transverse multiplanar examination of both feet in exact keeping with standardised scanning techniques (34, 35) on B-mode and power Doppler (PD) mode using a real-time scanner (Mylab 70 XVG, Esaote, Genoa, Italy) equipped with a multifrequency linear array transducer (6-18 MHz). B-mode and PD machine settings were optimised before the study and standardised for the whole study. These settings were as follows: B-mode frequency of 10-18 MHz, B-mode gain of 56-62%, Doppler frequency of 6.3–14.3 MHz, Doppler gain of 45–62%, low-wall filters, and pulse repetition frequency of 500–750 Hz, depending on the depth of the anatomic area. All US examinations were carried out in a dark room with temperature kept stable at 23°C. The patients rested for 15 minutes in the waiting room before the US

examinations. The patients were asked to avoid caffeine and alcohol intake, sport, and smoking for 8 hours before the US examinations and nonsteroidal anti-inflammatory drugs intake for 1 week before the US examinations. To reduce the possibility of bias, the patients were asked not to talk about their symptoms to the US examiner.

The following bilateral joints were investigated for the presence of intra-articular B-mode synovitis (either effusion or synovial hypertrophy), synovial PD signal, erosions, osteophytes and subluxation/luxation; tibiotalar (dorsal recess), talocalcaneal (medial and lateral recesses), talonavicular (dorsal recess), calcaneocuboid (lateral recess), tarsal and tarsometatarsal (dorsal recesses) and first to fifth MTP joints (dorsal recesses). The following bilateral tendons were assessed for the presence of B-mode tenosynovitis, Doppler tenosynovitis, and tendon damage: tibialis anterior, extensor halluces longus, extensor digitorum longus, tibialis posterior, flexor digitorumlongus, flexor halluces longus, peroneus brevis and peroneus longus. The Achilles tendon and the plantar fascia were examined bilaterally for the presence of enthesopathy, entheseal Doppler signal, enthesophytes, and damage. In addition, the presence of calcifications within the Achilles tendon, retrocalcaneal B-mode bursitis and PD signal within the retrocalcaneal bursa were also investigated.

B-mode synovitis was defined as the presence of abnormal hypoechoic intra-articular material. Bone erosion was defined as an intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes (35-39). Osteophyte was defined as a step up of bony prominence at the margin of the joint with or without acoustic shadow (35-39). Joint subluxation/luxation was defined as a loss of normal bone alignment. B-mode tenosynovitis was defined as an abnormal anechoic and/or hypoechoic (relative to tendon fibers) tendon sheath widening which can be related both to the presence of tenosynovial abnormal fluid and/or hypertrophy (35-39). Doppler tenosynovitis was defined as the presence of peri-tendinous PD signal within the synovial sheath, seen in two perpendicular planes, excluding normal nutrient vessels in mesotenon or vinculae, only if the tendon shows peritendinous synovial sheath widening on B-mode (35-39). Tendon damage was defined as an internal and/or peripheral absence of tendon fibers or as a complete interruption of the tendon fibers, seen in two perpendicular planes. This definition was also applied for plantar fascia damage. Enthesopathy was defined as an abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoicfoci consistent with calcifications), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity (35-39). Enthesophyte was defined as a step up of bony prominence at the enthesis, with or without acoustic shadow. B-mode bursitis was defined as an abnormal hypoechoic widening of the bursa.

US abnormalities were grouped into inflammatory (*i.e.* B-mode and Doppler synovitis and tenosynovitis) and structural (*i.e.* joint erosions, subluxation/luxation, osteophytes, enthesophytes, and tendon damage) involvement. Enthesopathy was analysed separately.

Statistical analysis

All statistical analysis was performed with SPSS 21.0 (IBM, Chicago, IL, USA). Quantitative variables were summarised as mean and standard deviation (SD), minimum and maximum and categorical variables as absolute frequencies and percentages. To compare quantitative variables between groups, the *t*-test for independent samples was used. To compare qualitative variables between groups, the Fisher exact test or chi-squared test were used. Haberman's adjusted standardised residuals were used to identify cells with observed frequencies higher or lower than expected.

The Mantel-Haenszel test was used to control the effect of unmatched age over the possible association between group and clinical and US findings; the sample was dichotomised in two strata by the median age and a common odds ratio was obtained. *p*-values associated to Mantel-Haenszel chi-squared and odds ratio of Mantel-Haenszel are shown in tables. The Breslow test was used to check homogeneity between age strata. *p*-values ≤0.05 were considered significant.

Results

Demographics

Most of the RA patients were female (48, 77.4%), mean (SD, range) age was 57.1 (12.4, 23–78) years, mean age by the time of RA diagnosis was 44.3 (12.9, 13–72) years, RA duration was 12.7 (7.1, 2.3–34) years and mean time of treatment with bDMARD was 6.1 (3.6, 0.4–15.9) years. Eight (12.9%) patients were obese. Thirty-five (56.4%) patients were RF positive, 45 (72.5%) patients were ACPA positive and 29 (46.7%) patients presented erosive disease.

Sixteen (25.8%) patients were treated with adalimumab, 20 (32.3%) with etanercept, 20 (32.3%) with rituximab, 4 (6.5%) with golimumab and 2 (3.2%) with certolizumab. The most commonly used csDMARDs were methotrexate (34, 54.8 %) and leflunomide (8, 12.9%). Five (5.1%) patients were taking oral corticosteroids (≤10 mg/day).

Sixty-two (83.8%) controls were female. Mean (SD, range) age was 43.2 (10.4, 24–70) years. Eight (10.8%) patients were obese.

Inappropriate shoes (*e.g.* soft foot wear, unclamped) were used by 31 (50.0%) RA patients compared with 25 (33.8%) controls (p=0.080). There was no significant difference in the use of appropriate shoe length/foot length relation between RA patients and controls (p=1.000). Nineteen (30.6%) patients with RA had needed podiatry treatment compared to 22 (29.7%) controls (p=1.000).There was no statistical difference in the proportion of obese subjects in either group [7 (11.3%) RA patients *vs.* 8 (10.8%) controls p=0.792].

Podiatric findings

Fifty-five (88.7%) RA patients and 63 (85.1%) controls had bilateral foot pain (p=1.000). Mean (SD) pain intensity was 5.48 (2.62) in the RA group and 5.64 (2.33) in the control group (p=0.722). Table I shows the type and

Table I. Type of pain and anatomic location in painful feet of RA patients and controls.

Pain	RA painful feet (n=117)	Control painful feet (n=137)	
	n (%)	n (%)	*p*
Type			
Mechanical	99 (84.6)	129 (94.2)	0.006
Mixed	14 (12.0)	4 (2.9)	
Neuropathic	4 (3.4)	4 (2.9)	
Location			
Ankle	8 (6.8)	3 (2.2)	<0.0005
Tarsalgia	11 (9.4)	13 (9.5)	
Metatarsalgia	81 (69.2)	91 (66.4)	
Talalgia	5 (4.3)	30 (21.9)	
Talalgia+metatarsalgia	12 (10.3)	0 (0.0)	

RA: rheumatoid arthritis.

Table II. Biomechanical findings in RA and control groups.

Variable	RA feet (n=124)		Control feet (n=148)				
	n	(%)	n	(%)	*p*	OR	CI95%
Rigid/limited mobility							
Ankle joint	41	(33.1)	24	(16.6)	0.024	2.17	(1.14-4.12)
Subtalar joint	46	(37.1)	21	(14.5)	0.001	3.31	(1.69-6.51)
1st MTP	84	(67.7)	67	(46.2)	0.101	1.67	(0.95-2.93)
Pathologic SHRT	26	(21.0)	7	(4.7)	0.008	4.74	(1.64-13.70)
Pathologic Jack's test	78	(63.4)	34	(23.0)	<0.0005	3.85	(2.15-6.88)
FPI Index							
Pronated	59	(47.6)	36	(24.5)	0.002	2.67	(1.46-4.78)
Supinated	29	(23.4)	16	(10.9)	0.029	2.57	(1.18-5.62)
Footprint							
Abnormal	83	(66.9)	73	(49.7)	0.033	1.91	(1.09-3.34)

RA: rheumatoid arthritis; MTP: metatarsophalangeal; SHRT: standing heel-rise test; FPI: foot postural index; *p*: Mantel-Haenszel chi-squared *p*-value; OR: Mantel-Haenszel odds ratio; CI: confidence interval.

Table III. US findings in RA and control groups.

Anatomical site	US findings	RA feet (n=124)		Control feet (n=148)				
		n	(%)	n	(%)	*p*	OR	CI95%
Talonavicular	Erosions	13	(10.5)	0	(0.0)	0.003		
Calcaneocuboid	Erosions	12	(9.7)	0	(0.0)	0.050		
1st MTP	Erosions	31	(25.0)	2	(1.4)	0.001	12.95	(2.58-65.13)
2nd-4th MTP	B-mode synovitis	62	(50.0)	51	(34.5)	0.001	2.72	(1.51-4.90)
	Osteophytes	12	(9.7)	0	(0.0)	0.001		
	Erosions	10	(8.1)	1	(0.7)	0.032	17.37	(1.27-237.85)
	Subluxation/luxation	12	(9.7)	2	(1.4)	0.033	4.02	(1.01-16.01)
5th MTP	B-mode synovitis	34	(27.4)	19	(12.8)	0.007	3.14	(1.46-6.73)
	Erosions	26	(21.0)	0	(0.0)	<0.0005		
Tibialis posterior tendon	B-mode tenosynovitis	7	(5.6)	1	(0.7)	0.009	18.81	(1.74-203.41)
Plantar fascia	Enthesophytes	10	(8.1)	0	(0.0)	0.031		

RA: rheumatoid arthritis; US: ultrasound; MTP: metatarsophalangeal joints; *p*: Mantel-Haenszel chi-squared *p*-value; OR: Mantel-Haenszel odds ratio; CI: confidence interval.

anatomic location of pain in the feet of RA patients and controls. According to the adjusted standardised residuals, mechanical pain was significantly less frequent in the RA group whereas mixed pain was significantly less frequent in the control group ($p<0.05$ for both). Talalgia, particularly heel pain, was more frequent in the control group whereas associated talalgia plus metatarsalgia was more frequent in the RA group ($p<0.05$ for both).

The distribution of toe deformities in the feet of RA patients and controls was as follows: lesser toe deformities (claw or hammer toe), 51 (41.2%) and 26 (17.6%) feet, respectively; hallux valgus, 53; (42.7%) and 16 (10.8%) feet, respectively; Taylor's bunion, 26 (21%) and 9(6.1%) feet, respectively ($p<0.0005$ for all).

Comparison of abnormal biomechanical findings between the RA group and the control group are displayed in Table II. Mantel-Haenszel chi-squared *p*-values showed significant association between group and biomechanical findings after controlling the age effect. Common Mantel-Haenszel odds ratio denoted how much greater were the age-adjusted odds of abnormal findings in the RA group with respects to the control group. There was a significant association between having RA and rigid/ limited mobility of the ankle and subtalar joints and pathologic SHRT, Jack's test, FPI and footprint. Regarding RCSP results, no significant differences were found between the control group and the RA group ($p=0.150$).

Plantar hyperkeratosis was significantly more frequent in the RA group (45 (36.39%) feet) than in the control group (23 (15.5%) feet) ($p=0.00$). However dorsal hyperkeratosis was significantly more frequent in controls (58 (39.2%) feet) than in RA patients (30 (24.2%) feet) ($p\leq0.05$).

US findings

B-mode synovitis was most frequently found in the 1st and any of the 2nd to 5th MTP joints of both RA and control subjects. Overall, the presence of B-mode synovitis in other joints (≤12 feet) and tendon abnormalities (≤7 feet) was low for both groups. Synovial PD signal was found in ≤3 feet and tenosynovial PD signal in ≤1 foot and only in RA patients. The joints most frequently showing osteophyte formation were the 1st MTP, talonavicular and calcaneocuboid joints for both groups. The joints most affected by bone erosions were the 1st and 5th MTP, almost all in RA patients. Retrocalcaneal bursitis, Achilles and plantar fascia enthesopa-

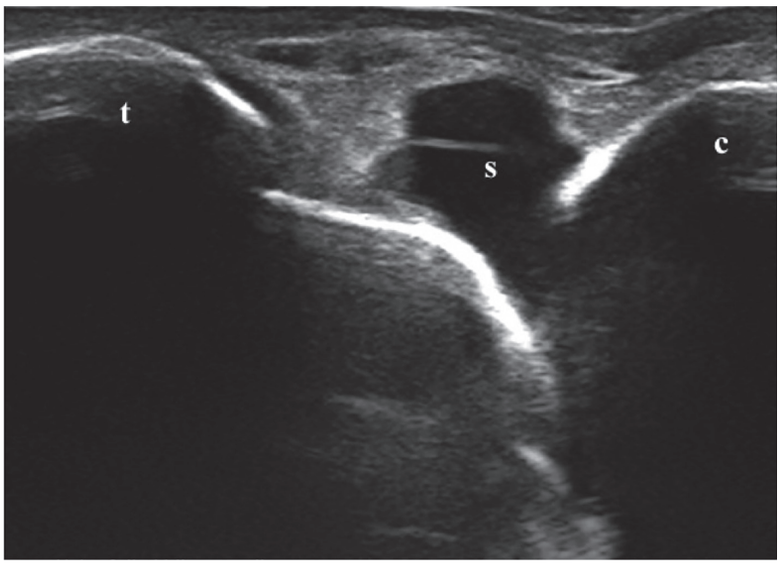

Fig. 1. Longitudinal ultrasound image of talocalcaneal B-mode synovitis (medial aspect) that shows abnormal hypoechoic intra-articular material (**s**). **t**, talus; **c**, calcaneous.

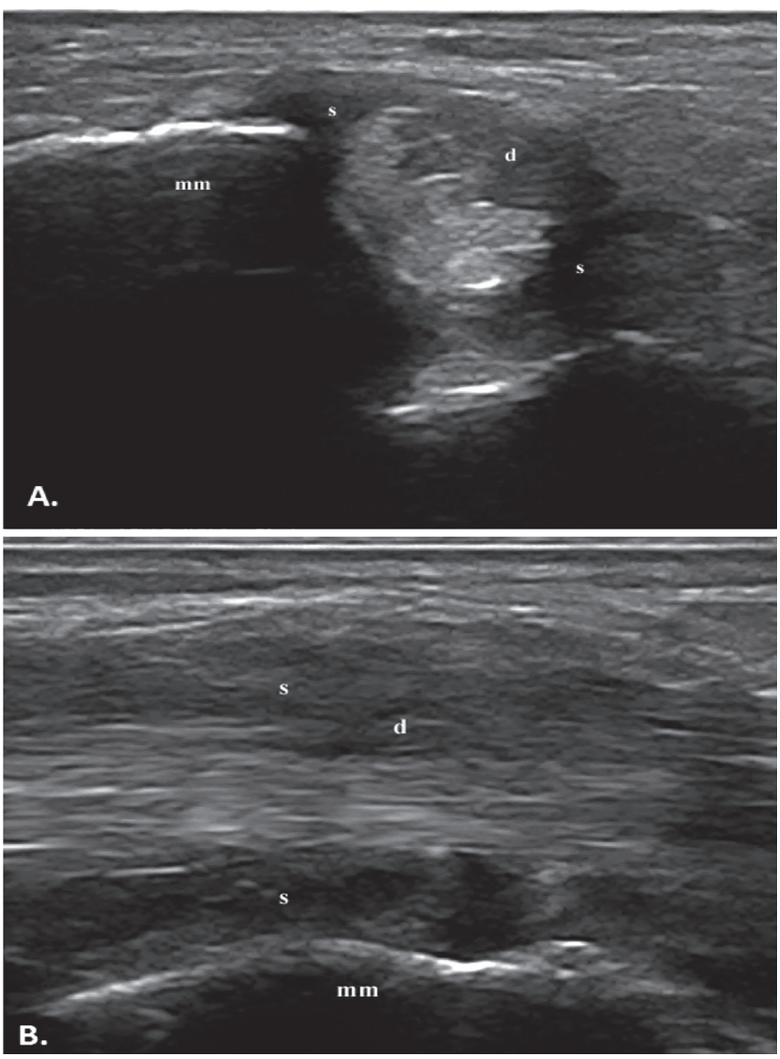

Fig. 2. (**A** and **B**). Transverse (**A**) and longitudinal (**B**) ultrasound image of a tibialis posterior B-mode tenosynovitis and damage that shows hypoechoic sheath widening (**s**) and a peripheral tendon defect (**d**). mm, medial malleolus.

thy and enthesophytes and Achilles tendon calcifications were rarely found (data not shown).

Table II displays the significant associations between US abnormalities and group, RA or control group. These were as follows: B-mode synovitis in the 2nd to 5th MTP joints; tibialis posterior B-mode tenosynovitis; bone erosions in the talonavicular and 1st to 5th MTP joints; osteophytes and subluxation/luxation in the 2nd to 4th MTP joints; and plantar fascia enthesophytes were significantly more frequent in RA patients than in controls. There were no significant differences in the remaining US abnormalities between both groups (data not shown). Representative images of US finding in RA feet are showed in Figures 1-2.

Relationship between US and biomechanical findings

Table IV shows the significant associations between US structural joint involvement and biomechanical abnormalities in RA patients. US structural involvement of MTP joints showed a significant association with limited tibiotalar and subtalar mobility, pathologic FPI, Jack's test and SHRT. US structural involvement of Chopart's joint, *i.e.* talonavicular and calcaneocuboid, was significantly associated with limited mobility of the 1st MTP joint as well as with abnormality of both Jack's test and SHRT. Subtalar structural involvement was significantly associated to those tests that evaluate this joint.

We found a significant association between US calcaneocuboid synovitis and a supinated FPI (p=0.040) and limited tibiotalar mobility (p=0.010). In addition, synovitis of the 4th MTP joint was significantly associated with limited tibiotalar (p=0.044) and subtalar (p=0.049) mobility.

No significant associations between US abnormalities and podiatric biomechanical abnormalities were found in controls (data not shown).

Discussion

To the best of our knowledge, this is the first study that has comprehensively assessed both biomechanical and US abnormalities in symptomatic feet of well

Table IV. Number (%) of US findings in feet with normal/abnormal biomechanical findings.

Joint	US structural status	RA feet, 124		
		Pronated FPI		
		Normal, n=65	Abnormal, n=59	*p*-value
2nd MTP	Abnormal	7 (10.8)	20 (33.9)	0.002
2nd MTP	Normal	58 (89.2)	39 (66.1)	
3rd MTP	Abnormal	2 (3.1)	13 (22.0)	0.002
3rd MTP	Normal	63 (96.9)	46 (78.0)	
4th MTP	Abnormal	1 (1.5)	9 (15.3)	0.006
4th MTP	Normal	64 (98.5)	50 (84.7)	
5th MTP	Abnormal	11 (16.9)	20 (33.9)	0.038
5th MTP	Normal	54 (83.1)	39 (66.1)	
		Supinated FPI		
		Normal, n=95	Abnormal, n=29	
2nd MTP	Abnormal	27 (28.4)	0 (0.0)	<0.0005
2nd MTP	Normal	68 (71.6)	29 (100.0)	
		Rigid/limited tibiotalar mobility		
		Normal, n=80	Abnormal, n=44	
1st MTP	Abnormal	24 (30.0)	23 (52.3)	0.003
1st MTP	Normal	56 (70.0)	21 (47.7)	
		Rigid/limited subtalar mobility		
		Abnormal, n=84	Abnormal, n=40	
Subtalar	Abnormal	4 (4.8)	8 (20.0)	0.026
Subtalar	Normal	80 (95.2)	32 (80.0)	
1st MTP	Abnormal	24 (28.6)	23 (57.5)	0.020
1st MTP	Normal	60 (71.4)	17 (42.5)	
		Rigid/limited 1st MTP mobility		
		Normal, n=42	Abnormal, n=82	
Talanovicular	Abnormal	7 (16.7)	31 (37.8)	0.023
Talanovicular	Normal	35 (83.3)	51 (62.2)	
Calcaneocuboid	Abnormal	4 (9.5)	32 (39.0)	0.001
Calcaneocuboid	Normal	38 (90.5)	50 (61.0)	
1st MTP	Abnormal	9 (21.4)	38 (46.3)	0.010
1st MTP	Normal	33 (78.6)	44 (53.7)	
		Jack's test		
		Normal, n=78	Normal, n=46	
Subtalar	Abnormal	0 (0.0)	12 (15.4)	0.004
Subtalar	Normal	46 (100.0)	66 (84.6)	
Talanovicular	Abnormal	3 (6.5)	35 (44.9)	<0.0005
Talanovicular	Normal	43 (93.5)	43 (55.1)	
Calcaneocuboid	Abnormal	4 (8.7)	32 (41.0)	<0.0005
Calcaneocuboid	Normal	42 (91.3)	46 (59.0)	
1st MTP	Abnormal	8 (17.4)	39 (50.0)	<0.0005
1st MTP	Normal	38 (82.6)	39 (50.0)	
3rd MTP	Abnormal	1 (2.2)	14 (17.9)	0.010
3rd MTP	Normal	45 (97.8)	64 (82.1)	
		SHRT		
		Normal, n=26	Normal, n=98	
Talanovicular	Abnormal	14 (53.8)	72 (73.5)	0.048
Talanovicular	Normal	12 (46.2)	26 (26.5)	
Calcaneocuboid	Abnormal	13 (50.0)	75 (76.5)	0.010
Calcaneocuboid	Normal	13 (50.0)	23 (23.5)	
1st MTP	Abnormal	8 (30.8)	69 (70.4)	<0.0005
1st MTP	Normal	18 (69.2)	29 (29.6)	

RA: rheumatoid arthritis; US: ultrasound; FPI: foot postural index; MTP: metatarsophalangeal joints; SHRT: standing heel-rise test.

controlled RA patients and compared them to controls without rheumatic or musculoskeletal disorders. We chose RA patients in remission or low disease activity treated with bDMARDs to minimise any possible distortion of RA clinically evident inflammation on results (40).

In line with previous studies, we found US-detected synovitis mainly in the MTP joints and tenosynovitis mainly in the tibialis posterior tendon in the RA population (6, 21). Despite the inactive/low disease status of our RA patients receiving bDMARDS, and despite pain intensity being similar in both RA patients and controls, we found significantly more feet presenting B-mode synovitis and tenosynovitis in the RA group than in the control group. Our results mirrored those of Sant'Ana Petterle *et al*. (22) who reported a significantly greater prevalence of subclinical US-detected synovitis in RA patients with asymptomatic feet compared to healthy controls. The presence of synovial or tenosynovial Doppler signal, although detected only in RA patients, was very low in our RA patients. As synovial Doppler signal is considered the US finding most related to aggressive inflammatory activity (14) this may indicate the relatively good control of disease activity in our population. Nevertheless, our findings lend support to the inclusion of the feet in the routine clinical and US assessments of RA activity, as previously suggested (41).

As expected, we found significantly more biomechanical and US-detected structural abnormalities in RA feet than in control feet. These can be interpreted as the sequelae of previous joint inflammation. Of particular note in our study was that US-detected structural involvement and synovitis were associated with biomechanical abnormalities only in RA patients. This fact may have important implications in the physiopathology of the RA foot. Biomechanical abnormalities in the control population may not be due to structural changes but mainly to functional disorders of the feet. Conversely, biomechanical abnormalities may be cause or consequence of structural changes and inflammation in RA patients. As the cross-sectional

nature of this study prevented us from investigating causality, further studies investigating this issue are warranted. If this is reflected in a wider context, RA patients in remission presenting foot complaints could be undertreated and may be at risk of further foot involvement progression. A podiatric clinical and US assessment of these patients with consequent podiatric (*i.e.* appropriate shoes, foot orthoses) and/or local/systemic additional treatment may optimise their management and improve their prognosis.

Some limitations in our study should be mentioned. The RA group was heterogeneous regarding demographics, and certain RA characteristics can influence biomechanical and US findings. In addition, the control group was younger than the RA group; however, we tried to offset this with the Mantel-Haenszel test. Furthermore, the absence of rheumatic or musculoskeletal disorders in controls was established only through anamnesis.

In conclusion, foot complaints experienced by RA patients in remission/low disease activity seemed to be associated to disease-related inflammation and biomechanical abnormalities. Podiatric and MSUS feet evaluation may well be valuable information when managing RA patients in daily practice.

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References

1. HOOPER L, BOWEN CJ, GATES L *et al*.: Prognostic indicators of foot-related disability in patients with rheumatoid arthritis: results of a prospective three-year study. *Arthritis Care Res* (Hoboken) 2012; 64: 1116-24.
2. ROME K, GOW PJ, DALBETH N, CHAPMAN JM: Clinical audit of foot problems in patients with rheumatoid arthritis treated at Counties Manukau District Health Board, Auckland, New Zealand. *J Foot Ankle Res* 2009; 2: 16.
3. RAO S, RISKOWSKI JL, HANNAN MT: Musculoskeletal conditions of the foot and ankle: assessments and treatment options. *Best Pract Res Clin Rheumatol* 2012; 26: 345-68.
4. FUCHS HA, BROOKS RH, CALLAHAN LF, PINCUS T: A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheumatol* 1989; 32: 531-7.
5. VAN DER LEEDEN M, STEULTJENS M, DEKKER JH, PRINS AP, DEKKER J: Forefoot joint damage, pain and disability in rheumatoid arthritis patients with foot complaints: the role of plantar pressure and gait characteristics. *Rheumatology* (Oxford). 2006; 45: 465-9.
6. VAN DER LEEDEN M, STEULTJENS MP, VAN SCHAARDENBURG D, DEKKER J: Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. *Arthritis Res Ther* 2010; 12: R3.
7. THOMAS MJ, RODDY E, ZHANG W, MENZ HB, HANNAN MT, PEAT GM: The population prevalence of foot and ankle pain in middle and old age: a systematic review. *Pain* 2011; 152: 2870-80.
8. SMOLEN JS, BREEDVELD FC, EBERL G *et al*.: Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheumatol* 1995; 38: 38-43.
9. WECHALEKAR MD, LESTER S, PROUDMAN SM *et al*.: Active foot synovitis in patients with rheumatoid arthritis: applying clinical criteria for disease activity and remission may result in underestimation of foot joint involvement. *Arthritis Rheumatol* 2012; 64: 1316-22.
10. OTTER SJ, LUCAS K, SPRINGETT K *et al*.: Comparison of foot pain and foot care among rheumatoid arthritis patients taking and not taking anti-TNFalpha therapy: an epidemiological study. *Rheumatol Int* 2011; 31: 1515-9.
11. SZKUDLAREK M, COURT-PAYEN M, STRANDBERG C, KLARLUND M, KLAUSEN T, OSTERGAARD M: Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. *Arthritis Rheumatol* 2001; 44: 2018-23.
12. WALTHER M, HARMS H, KRENN V, RADKE S, FAEHNDRICH TP, GOHLKE F: Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheumatol* 2001; 44: 331-8.
13. NAREDO E, BONILLA G, GAMERO F, USON J, CARMONA L, LAFFON A: Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis* 2005; 64: 375-81.
14. ANDERSEN M, ELLEGAARD K, HEBSGAARD JB *et al*.: Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. *Ann Rheum Dis* 2014; 73: 678-83.
15. BROWN AK, QUINN MA, KARIM Z *et al*.: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheumatol* 2006; 54: 3761-73.
16. SALEEM B, BROWN AK, KEEN H *et al*.: Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheumatol* 2009; 60: 1915-22.
17. NAREDO E, VALOR L, DE LA TORRE I *et al*.: Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? *Arthritis Care Res* (Hoboken) 2013; 65: 512-7.
18. DOHN UM, TERSLEV L, SZKUDLAREK M *et al*.: Detection, scoring and volume assessment of bone erosions by ultrasonography in rheumatoid arthritis: comparison with CT. *Ann Rheum Dis* 2013; 72: 530-4.
19. ZAYAT AS, ELLEGAARD K, CONAGHAN PG *et al*.: The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. *Ann Rheum Dis* 2014.
20. BOWEN CJ, CULLIFORD D, ALLEN R *et al*.: Forefoot pathology in rheumatoid arthritis identified with ultrasound may not localise to areas of highest pressure: cohort observations at baseline and twelve months. *J Foot Ankle Res* 2011; 4: 25.
21. BARN R, TURNER DE, RAFFERTY D, STURROCK RD, WOODBURN J: Tibialis posterior tenosynovitis and associated pes plano valgus in rheumatoid arthritis: electromyography, multisegment foot kinematics, and ultrasound features. *Arthritis Care Res* (Hoboken) 2013; 65: 495-502.
22. SANT'ANA PETTERLE G, NATOUR J, RODRIGUES DA LUZ K *et al*.: Usefulness of US to show subclinical joint abnormalities in asymptomatic feet of RA patients compared to healthy controls. *Clin Exp Rheumatol* 2013; 31: 904-12.
23. KEEN HI, REDMOND A, WAKEFIELD RJ *et al*.: An ultrasonographic study of metatarsophalangeal joint pain: synovitis, structural pathology and their relationship to symptoms and function. *Ann Rheum Dis* 2011; 70: 2140-3.
24. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheumatol* 1988; 31: 315-24.
25. HUSKISSON EC: Measurement of pain. *Lancet* 1974; 2: 1127-31.
26. BENNELL KL, TALBOT RC, WAJSWELNER H, TECHOVANICH W, KELLY DH, HALL AJ: Intra-rater and inter-rater reliability of a weight-bearing lunge measure of ankle dorsiflexion. *Aust J Physiother* 1998; 44: 175-80.
27. GASTWIRTH BW: Biomechanical examination of the foot and lower extremity. *In*: VALMASSY RL. *Clinical biomechanics of the lower extremites*. St. Louis. Mosby; 1996: 131-48.
28. SOBEL E, LEVITZ SJ, CASELLI MA *et al*.: Reevaluation of the relaxed calcaneal stance position. Reliability and normal values in children and adults. *J Am Podiatr Med Assoc* 1999; 89: 258-64.
29. GEIDEMAN WM, JOHNSON JE: Posterior tibial tendon dysfunction. *J Orthop Sports Phys Ther* 2000; 30: 68-77.
30. HALSTEAD J, REDMOND AC: Weight-bearing passive dorsiflexion of the hallux in standing is not related to hallux dorsiflexion during walking. *J Orthop Sports Phys Ther* 2006; 36: 550-6.
31. FASCIONE JM, CREWS RT, WROBEL JS: Dynamic footprint measurement collection technique and intrarater reliability: ink mat,

paper pedography, and electronic pedography. *J Am Podiatr Med Assoc* 2012; 102: 130-8.
32. CLELAND J, KOPPENHAVER S: Netter's orthopaedic clinical examination: an evidence-based approach. 2nd ed. Philadelphia, PA: Saunders; 2010.
33. REDMOND AC, CRANE YZ, MENZ HB: Normative values for the Foot Posture Index. *J Foot Ankle Res* 2008; 16. 10.1186/1757-1146-1-6.
34. BACKHAUS M, BURMESTER GR, GERBER T *et al*.: Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60: 641-9.
35. NAREDO E, RODRIGUEZ M, CAMPOS C *et al*.: Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheumatol* 2008; 59: 515-22.
36. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
37. IAGNOCCO A, CONAGHAN PG, AEGERTER P *et al*.: The reliability of musculoskeletal ultrasound in the detection of cartilage abnormalities at the metacarpo-phalangeal joints. *Osteoarthritis Cartilage* 2012; 20: 1142-6.
38. NAREDO E, D'AGOSTINO MA, WAKEFIELD RJ *et al*.: Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 1328-34.
39. BRUYN GA, HANOVA P, IAGNOCCO A *et al*.: Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. *Ann Rheum Dis* 2014; 73: 1929-34.
40. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
41. LANDEWÉ R, VAN DER HEIJDE D, VAN DER LINDEN S, BOERS M: Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006; 65: 637-41.