The feet in systemic lupus erythematosus; are we underestimating their involvement and functional impact?

R. Morales-Lozano[1], J. Martínez-Barrio[2], M.L. González-Fernández[1], F.J. López-Longo[2], J.G. Ovalles-Bonilla[2], L. Valor[2], I. Janta[2], J.C. Nieto[2], D. Hernández-Flórez[2], C.M. González[2], I. Monteagudo[2], J. Garrido[3], L. Carreño[2], E. Naredo[2]

[1]University Podiatry Clinic, Faculty of E.F.Podiatry Universidad Complutense de Madrid, Spain; [2]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [3]Department of Social Psychology and Methodology, Universidad Autónoma de Madrid, Spain.

Abstract

Objective

To evaluate biomechanical and ultrasound (US) abnormalities in SLE patients as compared with controls and to assess therelationship between these abnormalities and SLE activity.

Methods

Fifty-four consecutive female patients with SLE with and without foot pain and 60 female controls (30 with foot pain and 30 without foot pain) were recruited. SLE activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). SLE patients and controls blindly underwent a comprehensive podiatric, biomechanical and US evaluation of the feet. US assessment included detection of B-mode synovitis, tenosynovitis, enthesopathy, bone changes and synovial, tenosynovial and entheseal power Doppler (PD) signal.

Results

Thirty-one (57.4%) SLE patients had bilateral foot pain and 5 (9.3%) had unilateral foot pain. Metatarsalgia was the most common location for pain but without significant difference between groups ($p=0.284$). Toe joint deformities were significantly more common in SLE feet as compared with control feet ($p<0.0005$). SLE feet showed significantly more biomechanical abnormalities than control feet ($p<0.05$). B-mode synovitis in the tibiotalar joint was strongly associated with having SLE ($p<0.0005$) and the presence of synovial PD signal in the MTP joints was found only in painful feet of SLE patients. SLEDAI was significantly higher in patients with foot pain than in those with painless feet ($p=0.008$). However, SLEDAI did not discriminate between patients with and without biomechanical or US abnormalities.

Conclusion

SLE patients showed more biomechanical and US abnormalities in the feet than controls, which were not captured by standardised assessment of the disease activity.

Key words

foot, systemic lupus erythematosus, podiatry, biomechanics, ultrasound

Rosario Morales-Lozano, PhD
Julia Martínez-Barrio, MD
María Luz González-Fernández, PhD
Francisco Javier López-Longo, MD, PhD
Juan Gabriel Ovalles-Bonilla, MD
Lara Valor, MD, PhD
Iustina Janta, MD
Juan Carlos Nieto, MD
Diana Hernández-Flórez, MSc
Carlos M. González, MD, PhD
Indalecio Monteagudo, MD, PhD
Jesús Garrido, PhD, Prof.
Luis Carreño, MD, PhD, Assoc. Prof.
Esperanza Naredo, MD, PhD

Please address correspondence to:
Julia Martínez-Barrio,
Department of Rheumatology,
Hospital General Universitario
Gregorio Marañón,
Doctor Esquerdo 46,
28007 Madrid, Spain.
E-mail: juliamartinezbarrio@gmail.com

Received on October 18, 2015; accepted in revised form on January 7, 2016.

Funding: this study had no financial support

Competing interests:
R. Morales Lozano has received professor fees from Univadis;
M.L. Gonzalez-Fernandez has received professor fees from Univadis and Abbvie;
F.J. López-Longo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, MSD, Actelion, and also research funding from Abbvie and GSK;
L. Valor has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb and Pfizer.
Juan Carlos Nieto-González has received speaker fees from Abbvie, Roche Farma, Pfizer, MSD;
I. Monteagudo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB;
E. Naredo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, and Novartis.
The other co-authors have declared no competing interests.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide variety of multisystem clinical manifestations. Joint involvement in SLE is frequent and heterogeneous (1). Although hand involvement had been thoroughly studied (1-4), there are only a few studies describing the effect of the disease specifically on the ankle and foot (4-7). These studies have described a broad spectrum of foot involvement in SLE, which ranges from arthralgia to a deforming and/or erosive arthropathy, particularly in those patients with concomitant deforming arthropathy of the hands, with passively correctable joint deformities, rotational changes of the toes, hallux valgus, and subluxation/luxation of the metatarsophalangeal (MTP) joints with a consequent increase in plantar pressure and ulcers (5, 6). Tendon involvement (*i.e.* tenosynovitis and/or tendon rupture) has also been reported in SLE patients (7).

Within the last decade, musculoskeletal ultrasound (US) had become an accurate and sensitive bedside tool for joint and tendon assessment in inflammatory arthritis (8-16). In particular, some studies have described the presence of joint and tendon inflammation and structural damage in the hands of a high percentage of SLE patients with arthralgia without clinically detectable synovitis or SLE patients without clinical joint involvement (17-25). However, as for clinical studies, only a few studies have focused on the US abnormalities in the feet of SLE patients (26, 27).

The main objective of this cross-sectional study was to comprehensively evaluate biomechanical and US abnormalities in a population of SLE patients as compared with controls with and without foot complaints. The secondary objective was to assess the relationship between biomechanical and US abnormalities and SLE activity and the presence of autoantibodies in these patients.

Methods

Study population

Between January and February 2014, 54 consecutive SLE patients who fulfilled the inclusion and exclusion criteria were prospectively recruited from the Autoimmune Rheumatic Diseases Outpatient Clinic of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). Inclusion criteria were as follows; fulfilment of at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE (28, 29), female sex, age between 18 and 50 years, presence of foot pain (either unilateral or bilateral) for at least 3 months at inclusion or absence of foot pain during the course of the disease, and ability to participate in the study. Exclusion criteria were the following; previous foot surgery, sport overuse of the feet, severe foot trauma or injury, diabetes mellitus, neurological diseases, and congenital foot deformities.

Sixty controls aged between 18 and 50 years without a rheumatic or musculoskeletal disease were recruited from the Podiatry Clinic, Universidad Complutense de Madrid (Madrid, Spain). This control group consisted of 30 women with foot pain (either unilateral or bilateral) for at least 3 months at inclusion and 30 women who had never had foot pain. They met the same exclusion criteria as SLE patients.

All subjects were assessed blindly by three medical specialists who performed a complete clinical, podiatric and US evaluation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). Informed consent was obtained from all patients before study enrolment.

SLE clinical and laboratory assessment

Data on demographics, SLE duration and current treatment, presence of artrhritis at onset or during disease course, disease-related autoantibodies, rheumatoid factor (RF), and anti-citrullinated peptide antibodies (ACPAs) were collected from the Autoimmune Systemic Rheumatic Diseases Electronic Registry of the Department of Rheumatology (Hospital General Universitario Gregorio Marañón, Madrid, Spain). This registry includes data prospectively collected according to a pre-defined protocol at onset and during the course of the disease.

Non-organ-specific autoantibodies were investigated using indirect immunofluorescence (titers >1:80), which was performed according to standard procedures on cryostat sections of rat tissues (kidney, liver, and stomach) and in cultured HEp-2 cells (Mardx Diagnostics, Carlsbad, California, USA) using a fluorescein-conjugated from rabbit to human (DAKO, Copenhagen, Denmark). Titers of antibodies to double-stranded deoxyribonucleic acid (dsDNA) were measured using radioimmunoassay (Anti-dsDNA kit IM77, Kodak Clinical Diagnostics Ltd, Amersham, UK); levels higher than 20 IU/ml indicated a positive result. Anticardiolipin, anti-nRNP, anti-Sm, anti-Ro/SS-A, and anti-La/SS-B antibodies were investigated by enzyme-linked immunosorbent assay (ELISA). RF (>20 IU) was measured using nephelometry (Beckman, Fullerton, California, USA). ACPAs (>25 IU) [second generation commercial enzyme-linked immunosorbent assay (Immunoscan RA; Euro-Diagnostica, Malmö, Sweden] were also analysed.

Disease activity was assessed at study entry using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (30, 31). Disease activity measure by SLEDAI was divided into 4 categories: 0 points, no activity; 0–5 points, mild activity; 6–10 points, moderate activity; and >10 points, severe activity. In addition, body mass index (BMI) was calculated for patients and controls.

Podiatric assessment

All SLE patients and controls underwent a complete podiatric investigation by a Doctor in Podiatric Medicine (DPM) highly experienced (>20 years) in 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, whether they had treatment with foot orthoses, therapeutic footwear, or special foot care (*i.e* podiatry service) were recorded. Foot pain was quantified by a 0 (no pain) to 10 (severe pain) patient visual analogue scale (VAS) (32). Foot pain was classified as inflammatory (*i.e*. exacerbated by rest), mechanical (*i.e*. produced by movements), or mixed according to how it was described by the patient; inflammatory and mixed pain were analysed together. Pain on palpation was anatomically classified as ankle (*i.e*. tibiotalar joint) pain; tarsalgia (*i.e*. subtalar, Chopart's and Lisfrank's joints); metatarsalgia (*i.e*. MTP and interphalangeal joints); and talalgia (*i.e*. heel or fascial pain). The areas of plantar and dorsal hyperkeratosis and distal toe hyperaemia were recorded. Toe deformities (*i.e*. hallux valgus, hallux limitus/rigidus, Tailor's bunion, hammer and claw toes) were also recorded.

The biomechanical investigation consisted of several tests as follows; 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) according to the method of Bennell *et al*. (33). Abnormal mobility was considered as <25º–30º. For subtalar mobility assessment the patient lay prone on a flat examination table and the knee was placed in the frontal plane. The examiner then passively moved the subtalar joint into its end range of inversion and eversion. The average range of motion of the subtalar joint is 30 degrees: 20 degrees of inversion and 10 degrees of eversion. Abnormal mobility was considered as <5º–10º eversion and <10-20º inversion (34).

The Standing Heel-Rise Test (SHRT) consisted of placing the patient on tiptoe with both feet (double) and afterwards on each foot (simple). Failure to correct the heel varus position while performing the lift maneuver may indicate either presence of bone synostosis, subtalar joint involvement and/or tibialis posterior lesions as well as differentiates between a rigid and flexible flatfoot (35).

The forced dorsiflexion of the big toe or Jack's test was performed to distinguish a flexible foot from a rigid flat foot as well as to diagnose tibialis posterior dysfunction. This test was considered normal when on big toe elevation the longitudinal internal arch increased and the tibia and the calcaneus rotated externally (36).

The Foot Posture Index (FPI) consisted of quantifying standing foot posture in relaxed standing position according to 6 clinical criteria with a total score from -12 to +12. Each evaluated criterion was scored from -2 to 2 as follows: -2, if there were clear signs of supination; 0, if it was neutral; +2, if there were clear signs of pronation; both supination and pronation were consider are pathological (37).

The footprint was analysed using an ultralight Podoscope 50 cm x 50 cm (Herbitas, Foios, Valencia, Spain). While the patients were standing on the glass of the podoscope, the reflected footprint was visualised on the mirror. Footprint normality was defined as straight longitudinal axis, support of the toes and isthmus width of 1/3 of the forefoot (38).

US assessment

A podiatrist experienced in musculoskeletal US (*i.e*. >5 years) who was unaware of the group (SLE versus control), clinical and laboratory data performed a comprehensive US assessment of both feet of all SLE patients and controls. This assessment consisted of a systematic longitudinal and transverse multiplanar examination, according to a described standardised scanning technique (39, 40) on B-mode and power Doppler (PD) mode of the following bilateral joints; tibiotalar (dorsal recess), talocalcaneal (medial and lateral recesses), talonavicular (dorsal recess), calcaneocuboid (lateral recess), and first to fifth MTP joints (dorsal recesses). These joints were investigated for the presence of intra-articular B-mode synovitis (either effusion or synovial hypertrophy), synovial PD signal, erosions, and osteophytes. In addition, the following bilateral tendons were assessed for the presence of B-mode tenosynovitis, Doppler tenosynovitis, and tendon damage; tibialis anterior, extensor halluces longus, extensor digitorumlongus, 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. The presence of retrocalcaneal bursitis was also investigated.

A real-time scanner (Mylab 70 XVG,

Esaote, Genoa, Italy) equipped with a multifrequency linear array transducer (6-18 MHz) was used for the US assessment. 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 NSAIDs 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.

B-mode synovitis was defined as the presence of abnormal hypoechoic intra-articular material (41). Bone erosion was defined as an intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes (41). Osteophyte was defined as a step up of bony prominence at the margin of the joint, with or without acoustic shadow (42). B-mode tenosynovitis was defined as an abnormal anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening which can be related both to the presence of tenosynovial abnormal fluid and/or hypertrophy (43). 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 peri-tendinous synovial sheath widening on B-mode (43). Tendon damage was defined as an internal and/or peripheral absence of tendon fibres or as a complete interruption of the tendon fibres, seen in two perpendicular planes (44); 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 hyperechoic foci consistent with calcifications), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity (41). 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.

Statistical analysis

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 categorical 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. Two logistical regression models were developed. The first model studied factors associated to SLE, using as dependent variable 'group' (control/SLE) and independent variables podiatric and US abnormalities. The second model was run to study factors associated with pain in the feet of SLE patients, using as dependent variable 'pain' (yes/no) and independent variables podiatric and US abnormalities. Multivariate models using forced entry method and stepwise method were run. *p*-values <0.05 were considered as significant. All statistical analysis was performed with IBM SPSS Statistics 21.0.

Results

Demographics and pain characteristics in SLE patients and controls

Of the 54 SLE patients included in the study, 31 (57.4%) had bilateral foot pain, 5 (9.3%) had unilateral foot pain and 18 (33.3%) had not foot pain. Of the 30 controls with foot pain, 29 (96.7%) had bilateral pain and 1 (3.3%) had unilateral pain. The mean (SD) SLE duration was 13.2 (7.9) years. The mean (SD) age was 40.9 (10.1) years for SLE patients and 38.7 (15.2) for controls (p=0.376). There was no significant difference between SLE patients and controls in BMI [mean (SD) 23.0 (3.5) kg/m^2 for SLE patients and 23.9 (3.4) kg/m^2 for controls, p=0.132]. Foot pain intensity showed no significant difference between SLE patients [mean (SD), 6.7 (2.1)] and controls [mean (SD), 5.9 (2.2)] (p=0.129) with foot pain. At disease onset or during disease course, 38 (70.4%) patients had presented arthritis, of these, 3 (7.9%) patients also presented Jaccoud's arthropathy.

For SLE patients, mean (SD; range) SLEDAI was 5.33 (3.95; 0–22). Forty-seven (87.0%) SLE patients were treated with systemic glucocorticoids, 40 (74.1%) with antimalarials, 20 (37.0%) with azathioprine, 14 (25.9%) with mycophenolate, 14 (25.9%) with methotrexate, and 6 (11.1%) with rituximab. All (100%) SLE patients were positive for antinuclear antibodies, 42 (77.8%) for dsDNA antibodies, 15 (27.8%) for anti-RNP antibodies, 14 (25.9%) for anti-Sm antibodies, 22 (40.7%) for anti Ro/SSA antibodies, 13 (24.1%) for anti La/SSB, 16 (29.6%) for anticardiolipin antibodies, 20 (37.0%) for RF, and 4 (7.4%) for ACPAs.

Table I shows pain type and location in painful feet of SLE patients and controls. Inflammatory or mixed pain was significantly more frequent in SLE feet whereas mechanical pain was significantly more frequent in control feet (p<0.0005). In both groups, metatarsalgia was the most common location for pain on palpation but there was no significant difference between SLE and control painful feet in the distribution of pain location (p=0.284). There were no significant differences between SLE patients with and without arthritis at onset or during the disease course in pain type and location (p>0.005; data not shown).

Footwear, foot deformities and skin abnormalities in SLE patients and controls

There were no significant differences between SLE patients and controls in the use of inappropriate footwear [26 (48.1%) SLE patients *vs*. 21 (35%) controls, p=0.184], short length shoes [23 (42.6%) SLE patients *vs*. 20 (33.3%)

Table I. Pain type and locations in painful feet of SLE patients and controls.

	Painful feet in SLE group (n=67)	Painful feet in control group (n=59)	*p*-value
Type			
Mechanical, n (%)	27 (40.3)	55 (93.2)	
Inflammatory/mixed, n (%)	40 (59.7)	4 (6.8)	<0.0005
Location			
Metatarsalgia, n (%)	40 (59.7)	40 (67.8)	
Talalgia, n (%)	11 (16.4)	12 (20.3)	0.284
Tarsalgia, n (%)	10 (14.9)	6 (10.1)	
Tibiotalar, n (%)	6 (9.0)	1 (1.7)	

SLE: systemic lupus erythematosus.

controls, p=0.338] or use of podiatry service [15 (27.8%) SLE patients *vs*. 13 (21.7%) controls, p=0.516]. No subject used foot orthoses or therapeutic footwear in both groups.

Regarding skin abnormalities, plantar and dorsal hyperkeratosis (*i.e*. heloma/tiloma) and distal toe hyperaemia were significantly more frequent in SLE feet [10 (9.3%) and 11 (10.2%), respectively] than in control feet [2 (1.7%) and 0 (0.0%), respectively] (p=0.015 and p<0.0005, respectively). These differences remained significant for heloma with distal toe hyperaemia when painful SLE feet were compared with painful control feet [6 (9.0%) *vs*. 0 (0.0%), p=0.029)]. Among SLE patients, hyperkeratosis and distal toe hyperaemia were found only in painful feet.

There were no significant differences between SLE patients with or without arthritis at onset or during the disease course in the use of inappropriate footwear or regarding skin abnormalities (p>0.005; data not shown).

Table II displays toe joint deformities in the feet of SLE patients *versus* controls and in painful feet of SLE patients *versus* painful feet of controls. In general, toe joint deformities were significantly more common in SLE feet as compared with control feet. Hammer/claw toes, the most common joint deformity found in both groups, were significantly more frequent in total SLE feet as compared with total control feet. Hallux limitus/rigidus and Tailor's bunion were significantly more frequent in total SLE feet and painful SLE feet as compared with total control feet and painful control feet, respectively. There was no significant difference between both groups in the presence of hallux valgus. In the SLE group, the presence of one or more toe joint deformities was significantly more frequent in painful feet as compared with painless feet [47 (70.1%) *vs*. 13 (31.7%), p<0.0005].

Tailor's bunion was only found in SLE feet in patients with arthritis at onset or during the disease course [15 (19.7%), p=0.005)]. There were no other significant differences between SLE patients with or without arthritis at onset or during the disease course in toe joint deformities.

Biomechanical abnormalities in SLE patients and controls

Table III shows biomechanical abnormalities in the feet of SLE patients vs controls and in painful feet of SLE patients *versus* painful feet of controls. Overall, SLE feet showed significantly more limited tibiotalar mobility, patho-

Table II. Toe joint deformities in SLE patients and controls.

	SLE feet (n=108)	Control feet (n=120)	*p*-value	Painful SLE feet (n=67)	Painful control feet (n=59)	*p*-value
One or more joint deformities	60 (55.6)	35 (29.2)	<0.0005	47 (70.1)	31 (52.5)	0.046
Hallux valgus, n (%)	7 (6.5)	8 (6.7)	1.000	6 (9.0)	8 (13.6)	0.571
Hallux limitus/rigidus, n (%)	20 (18.5)	0 (0.0)	<0.0005	15 (22.4)	0 (0.0)	<0.0005
Tailor's bunion, n (%)	15 (13.9)	3 (2.5)	0.002	11 (16.4)	0 (0.0)	0.001
Hammer/claw toes, n (%)	26 (24.1)	13 (10.8)	0.009	19 (28.4)	12 (20.3)	0.310

SLE: systemic lupus erythematosus.

Table III. Biomechanical abnormalities in SLE patients and controls.

	SLE feet (n=108)	Control feet (n=120)	*p*-value	Painful SLE feet (n=67)	Painful control feet (n=59)	*p*-value
Limited ankle mobility, n (%)	26 (24.1)	12 (10.0)	0.007	24 (35.8)	12 (20.3)	0.075
Limited subtalar mobility, n (%)	10 (9,3)	13 (10.8)	0.826	10 (14.9)	11 (18.6)	0.636
Pathological SHRT, n (%)	8 (7.4)	7 (5.8)	0.790	8 (11.9)	3 (5.1)	0.216
Pathological Jack´s test, n (%)	36 (33.3)	25 (20.8)	0.037	28 (41.8)	17 (28.8)	0.141
Pronated FPI, n (%)	42 (38.9)	16 (13.3)	<0.0005	36 (53.7)	12 (20.3)	<0.0005
Supinated FPI, n (%)	15 (13.9)	3 (2.5)	0.002	7 (10.4)	3 (5.1)	0.334
Abnormal footprint, n (%)	59 (54.6)	37 (30.8)	<0.0005	42 (62.7)	28 (47.5)	<0.0005

SLE: systemic lupus erythematosus; SHRT: Standing Heel-Rise Test; FPI: Foot Postural Index-

Table IV. Biomechanical abnormalities in panful and painless feet of SLE patients.

	Painful feet (n=67)	Painless feet (n=41)	*p*-value
Limited ankle mobility, n (%)	24 (35.8)	2 (4.9)	<0.0005
Limited subtalar mobility, n (%)	10 (14.9)	0 (0.0)	0.012
Pathological SHRT, n (%)	8 (11.9)	0 (0.0)	0.023
Pathological Jack´s test, n (%)	28 (41.8)	8 (19.5)	0.021
Pronated FPI, n (%)	36 (53.7)	6 (14.6)	<0.0005
Supinated FPI, n (%)	7 (10.4)	8 (19.5)	0.252
Abnormal footprint, n (%)	42 (62.7)	17 (41.5)	0.046

SLE: systemic lupus erythematosus; SHRT: Standing Heel-Rise Test; FPI: Foot Postural Index.

Table V. US findings in SLE patients and controls.

	SLE feet (n=108)	Control feet (n=120)	*p*	Painful SLE feet (n=67)	Painful control feet (n=59)	*p*
Tibiotalar joint						
B-mode synovitis, n (%)	27 (25.0)	2 (1.7)	<0.0005	25 (37.3)	2 (3.4)	<0.0005
Synovial PD signal, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Erosions, n (%)	2 (1.9)	0 (0.0)	0.223	2 (3.0)	0 (0.0)	0.498
Osteophytes, n (%)	3 (2.8)	1 (0.8)	0.347	3 (4.5)	1 (1.7)	0.622
Talocalcaneal joint						
B-mode synovitis, n (%)	3 (2.8)	2 (1.7)	0.670	2 (3.0)	2 (3.4)	1.000
Synovial PD signal, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Erosions, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Osteophytes, n (%)	2 (1.9)	3 (2.5)	1.000	2 (3.0)	3 (5.1)	0.664
Talonavicular joint						
B-mode synovitis, n (%)	14 (13.0)	3 (2.5)	0.004	11 (16.4)	3 (5.1)	0.051
Synovial PD signal	1 (0.9)	0 (0.0)	0.474	1 (1.5)	0 (0.0)	1.000
Erosion	3 (2.8)	0 (0.0)	0.105	3 (4.5)	0 (0.0)	0.247
Osteophytes	14 (13.0)	10 (8.3)	0.285	13 (19.4)	10 (16.9)	0.819
Calcaneocuboid joint						
B-mode synovitis	5 (4.6)	1 (0.8)	0.104	3 (4.5)	1 (1.7)	0.622
Synovial PD signal	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Erosion	2 (1.9)	1 (0.8)	0.604	2 (3.0)	0 (0.0)	0.498
Osteophytes	4 (3.7)	6 (5.0)	0.752	4 (6.0)	5 (8.5)	0.733
1st MTP joint						
B-mode synovitis	31 (28.7)	26 (21.7)	0.226	19 (28.4)	25 (42.4)	0.134
Synovial PD signal	7 (6.5)	0 (0.0)	0.005	7 (10.4)	0 (0.0)	0.014
Erosion	4 (3.7)	2 (1.7)	0.426	4 (6.0)	2 (3.4)	0.684
Osteophytes	17 (15.7)	15 (12.5)	0.568	13 (19.4)	14 (23.7)	0.664
2nd-4th MTP joints						
B-mode synovitis	30 (27.8)	21 (17.5)	0.080	22 (32.8)	20 (33.9)	1.000
Synovial PD signal	4 (3.7)	0 (0.0)	0.049	4 (6.0)	0 (0.0)	0.122
Erosion	1 (0.9)	1 (0.8)	1.000	1 (1.5)	1 (1.7)	1.000
Osteophytes	4 (3.7)	0 (0.0)	0.049	4 (6.0)	0 (0.0)	0.122
5th MTP joint						
B-mode synovitis	9 (8.3)	7 (5.8)	0.605	7 (10.4)	7 (11.9)	1.000
Synovial PD signal	1 (0.9)	0 (0.0)	0.474	1 (1.5)	0 (0.0)	1.000
Erosion	1 (0.9)	0 (0.0)	0.474	0 (0.0)	0 (0.0)	
Osteophytes	9 (8.3)	0 (0.0)	0.001	8 (11.9)	0 (0.0)	0.007

SLE: systemic lupus erythematosus; PD: power Doppler; MTP: metatarsophalangeal.

logical Jack's test, abnormal FPI and abnormal footprint than control feet. When analysing only painful feet, pronated FPI and abnormal footprint were still significantly more frequent in SLE patients than in controls. Supinated FPI was only present in SLE feet in patients with arthritis at onset or during the disease course [11 (15%), p=0.003)]. There were no other significant differences between SLE patients with or without arthritis at onset or during the disease course in biomechanical abnormalities.

Table IV displays biomechanical abnormalities in painful and painless feet of SLE patients. Painful feet showed significantly more limited tibiotalar and subtalar mobility, pathological SHRT and Jack's test, pronated FPI and abnormal footprint than painless feet.

US findings in SLE patients and controls

Table V displays US findings in the feet of SLE patients *versus* controls and in painful feet of SLE patients *versus* painful feet of controls. B-mode synovitis in the 1st to 4th MTP joints was the most common abnormality in both SLE patients and controls; however there was no significant difference between groups in this finding. There were particular abnormalities significantly more frequent in total SLE feet than total control feet such as B-mode synovitis in the tibiotalar and talonavicular joints, synovial PD signal in the 1st–4th MTP joints, and osteophytes in the 2nd–5th MTP joints. Tibiotalar B-mode synovitis, synovial PD signal in the 1st MTP joint, and osteophytes in the 5th MTP joints were significantly more frequent in painful SLE feet than in painful control feet. When we compared only painful *vs*. painless SLE feet (data not shown), US findings significantly more frequent in painful feet were as follows; B-mode synovitis in the tibiotalar joint [25 (37.3%) painful feet *vs*. 2 (4.9%) painless feet, p<0.0005], synovial PD signal in the 1st MTP joint [7 (10.4%) painful feet *vs*. 0 (0.0%) painless feet, p=0.043], and osteophytes in the talonavicular joint [13 (19.4%) painful feet *vs*. 1 (2.4%) painless feet, p=0.016], Of particular interest was that synovial PD signal was found only in painful feet of SLE patients. Bone erosions were uncommon in both SLE patients and controls.

US involvement of tendons/plantar fascia was generally uncommon (data not shown). However, B-mode tenosynovitis of the tibialis posterior [8 (7.4%) SLE feet *vs*. 0 (0.0%) control feet, p=0.002], enthesopathy of the plantar fascia [11 (10.2%) SLE feet *vs*. 0 (0.0%) control feet, p<0.0005], and calcaneal enthesophytes at the plantar fascia attachment [5 (4.6%) SLE feet *vs*. 0 (0.0%) control feet, p=0.023] were found only in SLE feet.

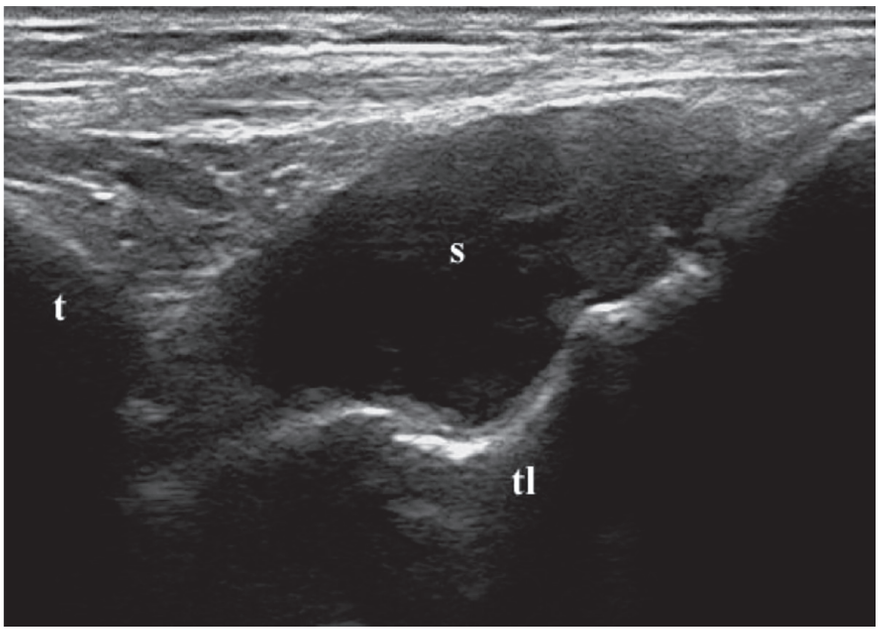

Fig. 1. Longitudinal ultrasound image of tibiotalar B-mode synovitis (dorsal aspect) that shows abnormal hypoechoic intra-articular material (s). t: tibia; tl. talus.

Osteophytes in the 5th MTP joint where more frequent in SLE feet from patients without arthritis at onset or during the disease course than in patients with arthritis [3 (18.8%) *vs*. 6 (3.9%), p=0.019)].

A representative US image in a SLE patient is shown in Figure 1.

Factors associated with SLE and foot pain

In the logistic regression analysis, among all variables, tibiotalar B-mode synovitis [OR=19.51 (CI95%, 4.38–87.00), p<0.0005], and abnormal FPI, either pronated [OR=4.82 (CI95%, 2.38–9.75), p<0.0005] or supinated [OR=11.25 (CI95%, 3.05–41.54), p<0.0005] were significantly associated with having SLE.

Regarding SLE patients, limited ankle mobility [OR=20.69 (CI95%, 3.90–109.94, p<0.0005], tibiotalar B-mode synovitis [OR=10.71 (CI95%, 2.10–54.69, p=0.004), and toe deformities [OR=7.12 (CI95%, 2.50–20.27, p<0.0005) were significantly associated with having foot pain.

Relationship between biomechanical and US abnormalities and SLE activity and autoantibodies

The SLEDAI was significantly higher in patients with foot pain [mean (SD) 6.31 (4.19)] than in those with painless feet [mean (SD) 3.39 (2.52)] (p=0.008). There was no significant difference in SLEDAI between SLE patients with and without toe joint deformities, skin abnormalities, biomechanical abnormalities or US pathological findings (data not shown). There was a significant association between having foot pain and SLEDAI> 0 (p=0.046). However, there was no significant association between having foot pain and SLEDAI<6/SLEDAI> 6 or SLEDAI <10/SLEDAI >10.

There was no significant association between having foot pain, toe joint deformities, skin abnormalities, biomechanical abnormalities or US pathological findings and positivity for dsDNA, anti-RNP, anti-Sm, anti Ro/SSA, anti La/SSB, or anticardiolipin antibodies, RF or ACPAs.

Discussion

A few studies have focused on foot involvement in SLE (4-7). However, the magnitude of this health problem has not been sufficiently addressed possibly because of the great anatomic and functional complexity of the foot, which has led to a lack of research on this field.

To the best of our knowledge, the present study is the first that comprehensively evaluated biomechanical and US abnormalities of the feet of a SLE population, with and without foot pain as compared with non-rheumatic controls with and without foot pain. Both groups were homogeneous in age, BMI, footwear appropriateness, podiatry service as well as in pain intensity for subjects with foot pain.

As expected, in general, foot pain was predominantly inflammatory or mixed in SLE patients, possibly due to the inflammatory nature of joint involvement in this disease whereas foot pain was mostly mechanical in controls.

In accordance with previously published data (26), MTP joints were the most common location for pain in SLE patients and for B-mode synovitis on US in total and painful feet of SLE patients. However, there were no significant differences in these variables between SLE patients and controls and between painful and painless feet in SLE patients. Thus, it seemed that the presence of metatarsalgia and B-mode US synovitis in MTP joints were neither characteristic of SLE nor specific for painful feet. Conversely, synovial PD signal in MTP joints, a marker of inflammatory activity, although less frequent in our population as in other studies (26), was present only in painful feet of SLE patients and discriminated between SLE patients and controls.

Of particular note was that in our study we found a strong association between having SLE and the presence of tibiotalar B-mode US synovitis as well as between having foot pain in SLE patients and again the presence of tibiotalar B-mode US synovitis and a limited mobility of this joint. To our knowledge, the specific involvement of the ankle joint detected by both clinical and US assessments has not been reported in SLE patients.

Several authors have described the presence of toe joint deformities secondary to non-erosive subluxations of MTP joints in SLE patients (3-5), which can produce metatarsalgia due to an excessive pressure of the soft tissues under the metatarsal heads. In accordance with this, we found that some toe joint deformities such as hammer/claw central toes, hallux limitus/rigidus, and Tailor's bunion in the 5th toe were signifi-

cantly more prevalent in SLE feet than control feet. In addition, the presence of toe joint deformities was strongly associated with having foot pain in SLE patients. Furthermore, the greater prevalence of osteophytes on US in the 2nd-5th MTP joints of SLE patients as compared with controls was consistent with the above clinical findings. These degenerative findings may be consequence of chronic toe joint subluxation in SLE patients. On the contrary, there was no significant difference between SLE and control groups in the presence of hallux valgus. Skin abnormalities, in particular heloma, tiloma and distal toe hyperaemia were more frequent in SLE patients than in controls as well as they were found only in painful SLE feet. This is not surprising as they are consequence of high pressure on the skin produced by malalignment of the toe joints.

Among the biomechanical tests, pathological Jack's test, FPI and footprint seemed to discriminate between SLE and control patients. In particular, pronated or supinated FPI was strongly associated with having SLE. In addition, abnormality of all biomechanical tests was associated with foot pain in SLE patients. These findings suggested that the biomechanics of the foot was impaired in SLE patients and this may contribute to foot pain in these patients. These biomechanical abnormalities may also be related with some US abnormalities predominant in SLE patients such as B-mode synovitis in the tibiotalar and talonavicular joints, B-mode tenosynovitis of the tibialis posterior tendon, or enthesopathy and enthesophytes at the calcaneal attachment of the plantar fascia.

Surprisingly, there were no differences between SLE patients with and without arthritis at onset or during the disease course except for Tailor's bunion and supinated FPI which were only found in the former. A few studies (45, 46) indicated that patients with a supinated arch are more likely to have Tailor's bunion because of the additional forces placed on the lateral aspect, while those with a pronated foot are more likely to have hallux valgus and overlapping toes. To the best of our knowledge there are no studies that have assessed the impact of MTP deformities on foot function in SLE. On the other hand, the fact that all SLE patients were receiving therapy can also explain the relatively low presence of other biomechanical abnormalities and inflammatory and structural US findings.

Interestingly, in our population the SLEDAI seemed to capture only the presence of foot pain but was not sensitive to the presence of toe joint deformities, and biomechanical and US abnormalities. This result may have relevant clinical implications since foot involvement, either symptomatic or asymptomatic, could be underestimated and undertreated in SLE patients. A routine clinical and US foot assessment with consequent appropriate local or systemic treatment may optimise the management of SLE patients. The presence of autoantibodies, including RF and ACPAs were associated neither with foot pain nor with podiatric and US abnormalities.

Some limitations in our study should be mentioned. The population size was relatively small. In addition, the cross-sectional nature of this study prevented us from addressing causality. Furthermore, the absence of rheumatic or musculoskeletal diseases in controls was established only through anamnesis.

In conclusion, SLE patients showed more biomechanical and US abnormalities in the feet than controls without SLE, which were not captured by standardised assessment of the disease activity. The presence of tibiotalar synovitis and sinovial PD signal in the MTP joints seemed to be specific for SLE as compared with a control group without rheumatic or musculoskeletal diseases. Early detection and treatment of foot involvement in SLE may optimise the management and improve the prognosis of these patients.

Key messages

- SLE patients showed more biomechanical and US feet abnormalities than controls without SLE.
- Biomechanical and ultrasound feet abnormalities were not captured by standardised assessment of disease activity.
- Early detection and treatment of SLE foot involvement may optimise management and improve prognosis.

References

1. ALARCÓN-SEGOVIA D, ABUD-MENDOZA C, DIAZ-JOUANEN E, IGLESIAS A, DE LOS REYES V, HERNÁNDEZ-ORTIZ J: Deforming arthropathy of the hands in systemic lupus erythematosus. *J Rheumatol* 1988; 15: 65-9.
2. FRANCESCHINI F, CRETTI L, QUINZANINI M, RIZZINI FL, CATTANEO R: Deforming arthropathy of the hands in systemic lupus erythematosus is associated with antibodies to SSA/Ro and to SSB/La. *Lupus* 1994; 3: 419-22.
3. VAN VUGT RM, DERKSEN RH, KATER L, BIJLSMA JW: Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. *Ann Rheum Dis* 1998; 57: 540-4.
4. REILLY PA, EVISON G, MCHUGH NJ, MADDISON PJ: Arthropathy of hands and feet in systemic lupus erythematosus. *J Rheumatol* 1990; 17: 777-84.
5. MIZUTANI W, QUISMORIO FP JR: Lupus foot: deforming arthropathy of the feet in systemic lupus erythematosus. *J Rheumatol* 1984; 11: 80-2.
6. WILLIAMS AE, CROFTS G, TEH LS: 'Focus on feet' – the effects of systemic lupus erythematosus: a narrative review of the literature. *Lupus* 2013; 22: 1017-23.
7. ALVES EM, MACIEIRA JC, BORBA E, CHIUCHETTA FA, SANTIAGO MB: Spontaneous tendon rupture in systemic lupus erythematosus: association with Jaccoud's arhropathy. *Lupus* 2010; 19: 247-54.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. ZAYAT AS, ELLEGAARD K, CONAGHAN PG *et al*.: The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 897-903.
14. BARN R, TURNER DE, RAFFERTY D, STURROCK RD, WOODBURN J: Tibialis posterior tenosynovitis and associated pes plano val-

gus in rheumatoid arthritis: electromyography, multisegment foot kinematics, and ultrasound features. *Arthritis Care Res* (Hoboken) 2013; 65: 495-502.
15. 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.
16. 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.
17. IAGNOCCO A, OSSANDON A, COARI G *et al*.: Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. *Clin Exp Rheumatol* 2004; 22: 621-4.
18. WRIGHT S, FILIPPUCCI E, GRASSI W, GREY A, BELL A: Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. *Lupus* 2006; 15: 501-6.
19. DELLE SEDIE A, RIENTE L, SCIRÈ CA *et al*.: Ultrasound imaging for the rheumatologist XXIV. Sonographic evaluation of wrist and hand joint and tendon involvement in systemic lupus erythematosus. *Clin Exp Rheumatol* 2009; 27: 897-901.
20. GABBA A, PIGA M, VACCA A *et al*.: Joint and tendon involvement in systemic lupus erythematosus: an ultrasound study of hands and wrists in 108 patients. *Rheumatology* (Oxford) 2012; 51: 2278-85.
21. TORRENTE-SEGARRA V, LISBONA MP, ROTÉS-SALA D *et al*.: Hand and wrist arthralgia in systemic lupus erythematosus is associated to ultrasonographic abnormalities. *Joint Bone Spine* 2013; 80: 402-6.
22. BUOSI AL, NATOUR J, MACHADO FS, TAKAHASHI RD, FURTADO RN: Hand ultrasound: comparative study between "no rhupus" lupus erythematosus and rheumatoid arthritis. *Mod Rheumatol* 2014; 24: 599-605.
23. YOON HS, KIM KJ, BAEK IW *et al*.: Ultrasonography is useful to detect subclinical synovitis in SLE patients without musculoskeletal involvement before symptoms appear. *Clin Rheumatol* 2014; 33: 341-8.
24. DREYER L, JACOBSEN S, JUUL L, TERSLEV L: Ultrasonographic abnormalities and inter-reader reliability in Danish patients with systemic lupus erythematosus - a comparison with clinical examination of wrist and metacarpophalangeal joints. *Lupus* 2015; 24: 712-9.
25. MOSCA M, TANI C, CARLI L *et al*.: The role of imaging in the evaluation of joint involvement in 102 consecutive patients with systemic lupus erythematosus. *Autoimmun Rev* 2015; 14: 10-5.
26. IAGNOCCO A, CECCARELLI F, RIZZO C *et al*.: Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. *Rheumatology* (Oxford) 2014; 53: 465-72.
27. LINS CF, SANTIAGO MB: Ultrasound evaluation of joints in systemic lupus erythematosus: a systematic review. *Eur Radiol* 2015; 25: 2688-92.
28. TAN EM, COHEN AS, FRIES JF *et al*.: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
29. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
30. BOMBARDIER C, GLADMAN DD, UROWITZ MB, CARON D, CHANG CH: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35: 630-40.
31. GLADMAN DD, IBAÑEZ D, UROWITZ MB: Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288-91.
32. HUSKISSON EC: Measurement of pain. *Lancet* 1974; 2: 1127-31.
33. 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.
34. GASTWIRTH BW: Biomechanical examination of the foot and lower extremity. *In*: VALMASSY RL. *Clinical biomechanics of the lower extremities*. St. Louis:. Mosby; 1996: 131-148.
35. GEIDEMAN WM, JOHNSON JE: Posterior tibial tendon dysfunction. *J Orthop Sports Phys Ther* 2000; 30: 68-77.
36. 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.
37. REDMOND AC, CRANE YZ, MENZ HB: Normative values for the Foot Posture Index. *J Foot Ankle Res* 2008; 1: 6.
38. FORRIOL F, PASCUAL J: Footprint analysis between three and seventeen years of age. *Foot Ankle* 1990; 11: 101-4.
39. BACKHAUS M, BURMESTER GR, GERBER T *et al*.: Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60: 641-9.
40. 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 Rheum* 2008; 59: 515-22.
41. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
42. 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.
43. 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.
44. 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.
45. HAGEDORN TJ, DUFOUR AB, RISKOWSKI JL *et al*.: Foot disorders, foot posture, and foot function: The Framingham Foot Study. *PLoS ONE* 2013; 8: e74364.
46. GOLIGHTLY YM, HANNAN MT, DUFOUR AB, HILLSTROM HJ, JORDAN JM: Foot Disorders Associated with Over-Pronated and Over-Supinated Foot Function: The Johnston County Osteoarthritis Project. *Foot Ankle Int* 2014; 35: 1159-65.