ULTRASOUND-DETECTED SYNOVITIS OF THE FOREFOOT IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS, UNLIKE THAT OF THE HAND, DOES NOT CORRELATE POSITIVELY WITH 28-JOINT DISEASE ACTIVITY SCORES

RYOTA HARA[1,2], YUSUKE OZAKI[1,2], NAOKI SHIMMYO[1], YASUHIRO AKAI[1], TAKASHI FUJIMOTO[1] and YASUHITO TANAKA[1,2]

Rheumatology Clinic, Nara Medical University[1]

Department of Orthopaedic Surgery, Nara Medical University[2]

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Abstract

Objective : This study aimed to clarify the relationship between the ultrasound (US)-detected forefoot synovitis and systemic disease activity and functional disability in patients with early rheumatoid arthritis (ERA).

Methods : Thirty-eight ERA patients (6 men, 32 women) prior to initiation of tight-control treatment were included. Semiquantitative US assessment for bilateral finger, wrist, and forefoot joints was conducted using gray-scale (GS) and power Doppler (PD), and each summation was defined as hand, foot, and total scores. The accuracy of US based on the physical examination for the metatarsophalangeal (MTP) joints was determined. The relationshio between each US score and composite measures using 28-joint counts, serum biomarkers, and patient-reported functional impairment scores was analyzed.

Results : Based on MTP joint swelling and tenderness, for GS and PD scores ≥ 1, the positive predictive value was low (GS: 16.0%, 12.5%; PD: 38.5%, 17.5%). Hand US scores, especially in hand PD scores, showed a significant moderate positive correlation with disease activity scores and biomarkers; however, foot US scores showed no positive correlation with any factor. The results were robust in multivariate analyses that incorporated each score and were adjusted for age.

Conclusions : US-detected forefoot synovitis may not be reflected in the composite disease activity scores not including direct forefoot assessment in ERA patients.

Key words : metatarsophalangeal joint, early rheumatoid arthritis, composite measure, ultrasound, synovitis

Introduction

A recent treatment goal for rheumatoid arthritis (RA) has been to evaluate disease activity on the basis of the treat-to-target concept and to achieve clinical remission[1]. A treatment strategy and target of treatment are determined using composite measures of disease activity, including

joint findings. The 28-joint Disease Activity Score (DAS28) [2], Simplified Disease Activity Index (SDAI) [3], and Clinical Disease Activity Index (CDAI) [4] are generally used in these evaluations, but the feet not included. In particular, the frequency of the initial RA presentation in the forefoot is as high as 45%, followed by the finger [5]. A previous report concluded that inclusion of the ankles and forefeet in the assessment of clinical remission is not required although the inclusion of these joints in the examination is recommended [6]. Ankle joint involvement contributes to worsening of patient global assessment scores (PtGA) in patients with a swollen joint count of ≤ 1 and tender joint count of ≤ 1 in the 28 joints; in contrast, forefoot synovitis does not affect PtGA, nor C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels [7]. From the above, clinical forefoot synovitis, which is different from ankle synovitis, does not affect composite indices. Moreover, clinical interobserver agreement for joint involvement of the forefoot, especially in detecting joint swelling, is extremely poor [8].

Ultrasonography can visualize joint inflammation more reliably than physical examination 9), and its value is demonstrated in a site that is difficult to evaluate by physical examination, such as the forefoot. A high level of intraobserver and interobserver agreement was reported for US effusion, synovitis, and power Doppler (PD) signals even in the forefoot [9]. Asymptomatic synovitis was detected in 17% of the patients by ultrasonography, of whom 79% had metatarsophalangeal (MTP) joint involvement [10]. To clarify the relationship between US-detected synovitis of the forefoot and the systemic disease activity and functional disability of early RA (ERA) before initiation of a strict control, we analyzed the correlation between those variables after categorizing them for the hand and foot.

Patients and methods

Patients

Thirty-eight early RA patients (6 men, 32 women) with disease duration of 2 years or less admitted in our hospital between December 2010 and November 2012 were included. All patients met the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria [11]. The patients' age, sex, disease duration, use of disease-modifying antirheumatic and nonsteroidal anti-inflammatory drugs (NSAIDs), and oral use of glucocorticoids were evaluated.

Clinical assessment included swelling and tenderness of 38 joints, including bilateral glenohumeral, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP), interphalangeal (IP), and MTP joints and the evaluator's global assessment (EGA). Laboratory markers included ESR, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), CRP, and matrix metalloproteinase-3 (MMP-3). PtGA and modified Health Assessment Questionnaire (mHAQ) [12] scores were investigated.

This study was approved by the ethics committee of Nara Medical University. The study was conducted in accordance with the Declaration of Helsinki.

US assessment

US assessment of bilateral IP, PIP, MCP, wrist, and MTP joints was performed by single sonographer (RH) using HI VISION AVIUS (5-13MHz; Hitachi Aloka Medical, Ltd., Tokyo, Japan)

with a linear-type probe. Each joint was evaluated by dorsal longitudinal imaging. The wrists were evaluated on the radial, medial, and ulnar sides. A semiquantitative evaluation (grades 0–3) was conducted using gray-scale (GS) and PD US techniques [13]. Each joint was scored for GS and PD on a semiquantitative scale from 0 to 3 [9]. Synovial hypertrophy in GS was graded as follows: grade 0 = absence, no synovial thickening; grade 1 = mild, minimal synovial thickening filling the angle between the periarticular bones without bulging over the line linking the tops of the bones; grade 2 = moderate, synovial thickening bulging over the line linking the tops of the periarticular bones but without extension to at least one bone diaphysis; grade 3 = marked, synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to at least one of the bone diaphyses. PD signals were graded as follows: grade 0 = absence, no synovial flow; grade 1 = mild, single-vessel signals; grade 2 = moderate, confluent signals in less than half of the synovial area; and grade 3 = marked, signals in more than half of the synovial area. For the hand (bilateral IP, PIP, and wrist joints), foot (bilateral MTP joints), and total joints (hand + foot), each summation was defined as a hand GS (0–78) and PD (0–78), foot GS (0–30) and PD (0–30), and total GS (0–108) and PD (0–108) score.

Statistical analysis

Continuous and categorical variables were treated with the Mann-Whitney U test and Chi-square test for the comparison with the groups. The diagnostic accuracy of GS-positive (GS score ≥ 1) and PD-positive joints (PD score ≥ 1) was determined based on joint swelling and tenderness observed on physical examination of the MTP joint. The total, hand, and foot GS and PD scores, composite measurements, levels of serum markers such as CRP and MMP-3, and mHAQ scores were compared using Spearman's rank correlation coefficient. To demonstrate the independent associations of hand and foot US score with each of the global clinical and functional measures, we included them and age as covariates and performed multiple linear regression analysis. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical and ultrasonographic characteristics of patients

The characteristics of the patients are shown in Table 1. Among 38 ERA patients, the median (Interquartile range (IQR)) age was 58.5 (49.3-65.8), 32 patients (84.2%) were female. Twenty-nine patients (76.3%) were RF-positive, 29 patients (76.3%) were ACPA-positive, and the median (IQR) DAS28-ESR, SDAI, and CDAI was 5.1 (4.1-5.9), 23.6 (14.2-29.1), and 21.8 (13.6-27.5) respectively. Thirty-two patients (84.2%) were receiving NSAIDs and 12 patients (31.6%) were receiving oral glucocorticoid. With GS ultrasonography, the median hand GS, foot GS, and total GS scores were 16.0 (11.3–24.8), 6.0 (3.3-9.0), and 24.0 (15.3–30.8), respectively. With PD ultrasonography, the median hand PD, foot PD, and total PD scores were 10.0 (6.3–20.0), 0.0 (0.0-2.0), and 12.0 (8.0–20.0), respectively (Table 1). In a two-group comparison of patients with and without forefoot ultrasound synovitis defined by PD>1, the ultrasound-positive group tended to have statistically sig-

Table 1. Characteristics of patients.

		US-detected synovitis of MTP joint		
	Overall	Positive (PD≥1)	Negative (PD=0)	*p* Value
N	38	16 (42.1)	22 (57.9)	
Age (years)	58.5 (49.3-65.8)	57.0 (48.3-63.0)	61.0 (49.3-66.8)	.60
Female, n (%)	32 (84.2)	15 (93.8)	17 (77.3)	.36
Disease Duration (month)	6.5 (3.0-11.8)	7.5 (3.0-14.5)	6.5(3.3-9.5)	.64
RF positive, n (%)	29 (76.3)	15 (93.8)	14 (63.6)	.08
ACPA positive, n (%)	29 (76.3)	14 (87.5)	15 (68.2)	.32
28- swollen joint count	6.0 (2.0-8.8)	4.0 (1.8-5.8)	7.5 (3.8-9.8)	.08
28-tender joint count	4.0 (2.0-6.8)	3.0 (0.8-4.0)	6.0 (2.3-8.0)	.04
MTP-swollen joint count	0.0 (0.0-2.0)	0.0 (0.0-2.5)	0.0 (0.0-1.0)	.47
MTP-tender joint count	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	.40
PtGA (mm)	50.0 (31.5-60.0)	50.0 (13.8-52.5)	47.5 (37.0-60.0)	.60
EGA (mm)	50.0 (40.0-67.5)	50.0 (20.0-60.0)	60.0 (42.5-77.5)	.09
CRP (mg/dl)	1.1 (0.2-1.8)	0.2 (0.2-1.2)	1.2 (0.8-2.1)	.02
MMP-3 (ng/ml)	158.9 (60.8-208.8)	73.8 (48.7-147.5)	130.0 (85.0-245.5)	.06
ESR (mm/hr)	49.0 (25.0-72.3)	38.5 (22.0-60.5)	57.5 (33.3-83.3)	.12
DAS28-ESR	5.1 (4.1-5.9)	4.8 (3.5-5.3)	5.5 (4.8-6.1)	.06
SDAI	23.6 (14.2-29.1)	16.8 (6.7-23.8)	26.2 (16.2-30.6)	.06
CDAI	21.8 (13.6-27.5)	16.0 (6.1-23.5)	24.5 (15.8-28.4)	.06
mHAQ	0.3 (0.1-0.4)	0.1 (0.0-0.3)	0.3 (0.2-0.5)	.05
NSAIDs, n (%)	32 (84.2)	14 (87.5)	18 (81.8)	.98
Glucocorticoid, n (%)	12 (31.6)	3 (18.8)	9 (40.9)	.18
csDMARDs, n (%)	18 (47.4)	8 (50.0)	10 (45.5)	1.00
Total GS score	24.0 (15.3-30.8)	25.5 (8.0-103.0)	23.5 (10.0-41.0)	.82
Total PD score	12.0 (8.0-20.0)	12.0 (2.0-60.-)	12.0 (5.0-25.0)	.78
Hand GS score	16.0 (11.3-24.8)	15.0 (5.0-76.0)	16.0 (10.0-33.0)	.56
Hand PD score	10.0 (6.3-20.0)	8.5 (0.0-48.0)	12.0 (5.0-25.0)	.18
Foot GS score	6.0 (3.3-9.0)	8.0 (3.0-27.0)	4.5 (0.0-18.0)	.009
Foot PD score	0.0 (0-2.0)	2.0 (1.0-12.0)	-	-

Data are shown as median (Interquartile range) or number (percentage).

ACPA: anti-cyclic citrullinated peptide antibody; CDAI: clinical disease activity index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; DAS28-ESR: 28-joint Disease Activity Score using the erythrocyte sedimentation rate; ESR: erythrocyte sedimentation rate; EGA: evaluator global assessment; mHAQ: modified health assessment questionnaire; MMP-3: matrix metalloproteinase-3; MTP: metatarsophalangeal; NSAIDs: nonsteroidal antiinflammatory drugs; PD: power Doppler; PtGA: patient global assessment; RF: rheumatoid factor; SDAI: simplified disease activity index; US: ultrasound.

nificantly lower CRP and number of tender joints in the 28-joint evaluation, and higher disease activity and physical disability scores. The GS score on foot ultrasound was statistically higher in the PD-positive group.

Diagnostic performance for US detection of synovitis in MTP joints

On physical examination of 380 bilateral MTP joints, 23, 14, 10, and 333 joints showed both swelling and tenderness, only swelling, only tenderness, and no swelling and tenderness, respectively. Of the 333 joints considered normal on physical examination, 116 (30.5%) and 24 (6.3%) showed a GS score of ≥ 1 and PD score of ≥ 1. Based on the swelling of the bilateral MTP joints, for a GS score of ≥ 1, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 60.5%, 64.6%, 16.0%, 93.6%, and 64.2%, respectively. For a PD score of ≥ 1, the sensitivity, specificity, PPV, NPV, and accuracy were 40.5%, 92.7%, 37.5%, 93.5%, and 87.6%, respectively. Based on tenderness, for a GS score of ≥ 1, the sensitivity, specificity, PPV, NPV, and accuracy were 54.5%, 63.7%, 12.5%, 93.6%, and 62.9%, respectively. For a PD score of ≥ 1, the sensitivity, specificity, PPV, NPV, and accuracy were21.2 %, 90.5%, 17.5%, 92.4%, and 84.5%, respectively (Table 2).

Table 2. Diagnostic performance of ultrasound-detected synovitis of metatarsophalangeal joints.

	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	Accuracy(%)
A. Swollen joint					
GS≥1	60.5	64.6	16.0	93.6	64.2
PD≥1	40.5	92.7	37.5	93.5	87.6
B. Tender joint					
GS≥1	54.5	63.7	12.5	93.6	62.9
PD≥1	21.2	90.5	17.5	92.4	84.5

GS: gray-scale; PD: power Doppler; NPV: negative predictive value; PPV: positive predictive value.

Associations between clinical parameters and US scores

Using Spearman's rank correlation coefficient, we calculated each correlation for DAS28-ESR, SDAI, CDAI, CRP level, MMP-3 level, PtGA score, and mHAQ score, with the total, hand,

Table 3. Correlation between gray-scale, power-Doppler scores and composite measures using 28-joint counts, serum biomarkers and patient-reported outcomes.

	DAS28-ESR	SDAI	CDAI	CRP	MMP-3	PtGA	mHAQ
Total GS	ρ=0.28, p=.09	ρ=0.40, p=.01	ρ=0.36, p=.03	ρ=0.39, p=.02	ρ=0.36, p=.02	ρ=0.25, p=.12	ρ=0.23, p=.16
Hand GS	ρ=0.40, p=.01	ρ=0.50, p=.002	ρ=0.45, p=.005	ρ=0.39, p=.01	ρ=0.47, p=.003	ρ=0.26, p=.11	ρ=0.17, p=.32
Foot GS	ρ=0.21, p=.20	ρ=0.05, p=.76	ρ=0.04, p=.83	ρ=0.11, p=.53	ρ=0.001, p=.99	ρ=0.14, p=.41	ρ=0.14, p=.41
Total PD	ρ=0.42, p=.009	ρ=0.45, p=.005	ρ=0.40, p=.01	ρ=0.48, p=.002	ρ=0.49, p=.002	ρ=0.19, p=.25	ρ=0.18, p=.29
Hand PD	ρ=0.49, p=.002	ρ=0.52, p<.001	ρ=0.47, p=.003	ρ=0.58, p=.003	ρ=0.58, p<.001	ρ=0.21, p=.21	ρ=0.24, p=.14
Foot PD	ρ=-0.27, p=.10	ρ=-0.27, p=.10	ρ=-0.27, p=.10	ρ=-0.33, p=.04	ρ=-0.27, p=.10	ρ=-0.09, p=.59	ρ=-0.28, p=.09

CDAI: clinical disease activity index; CRP: C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score using the erythrocyte sedimentation rate; GS: gray-scale; mHAQ: modified health assessment questionnaire; MMP-3: matrix metalloproteinase-3; PD: power Doppler; PtGA: patient global assessment; SDAI: simplified disease activity index.

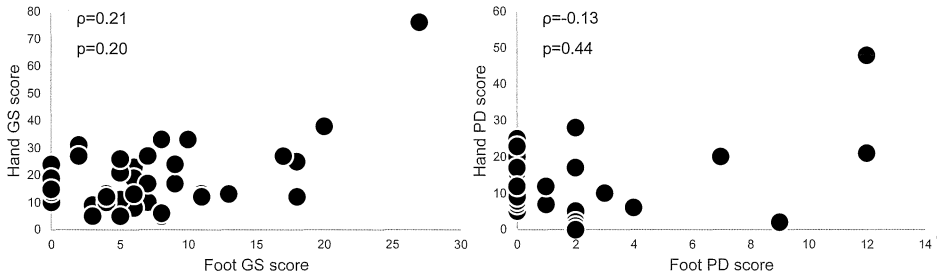

Fig. 1. Correlation between hand and foot ultrasonographic score in gray-scale (A) and in power-Doppler (B). The Spearman's rank correlation coefficient (p) and p value are shown above each scatter plot.

Table 4. Multiple linear regression analysis in age-adjusted models to exclude each effect of hand and foot US-detected synovitis

	DAS28-ESR		SDAI		CDAI		CRP		MMP-3		PtGA		mHAQ	
	β(SE)	*p* Value	β(SE)	*p* Value	β(SE)	*p* Value	β(SE)	*p* Value	β(SE)	*p* Value	β(SE)	*p* Value	β(SE)	*p* Value
Hand GS	0.07 (0.02)	<.001	0.73 (0.16)	<.001	0.67 (0.14)	<.001	0.05 (0.03)	.07	8.6 (1.7)	<.001	0.45 (0.36)	.23	0.006 (0.005)	.24
Foot GS	-0.08 (0.04)	.03	-0.47 (0.32)	.15	-0.48 (0.30)	.11	0.01 (0.06)	.89	-2.4 (3.6)	.50	-0.34 (0.76)	.66	-0.002 (0.001)	.87
Hand PD	0.09 (0.02)	<.001	0.93 (0.19)	<.001	0.82 (0.18)	<.001	0.11 (0.03)	.002	10.9 (2.1)	<.001	0.61 (0.44)	.17	0.01 (0.006)	.05
Foot PD	-0.11 (0.06)	.08	-0.99 (0.56)	.08	-0.84 (0.52)	.12	-0.15 (0.10)	0.15	1.0 (6.2)	.87	-1.6 (1.3)	.24	-0.02 (0.02)	.25

CDAI: clinical disease activity index; CRP: C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score using the erythrocyte sedimentation rate; GS: gray-scale; mHAQ: modified health assessment questionnaire; MMP-3: matrix metalloproteinase-3; PD: power Doppler; PtGA: patient global assessment; SDAI: simplified disease activity index.

and foot GS scores and total, hand, and foot PD scores (Table 3). Total GS and PD and hand GS and PD scores had a statistically significant positive correlation with SDAI and DAS28-ESR, which were composite measures of disease activity, and CRP level and MMP-3, which were serum markers. However, foot GS and PD scores did not show any positive correlation with SDAI, DAS28-ESR, CRP level, MMP-3 level, and each hand US score (Figure 1). PtGA and mHAQ scores showed no correlation with any US score. To eliminate mutual influences, the analysis was performed using multiple linear regression analysis that also adjusted for age, but showed little change in the relationship between hand and foot US scores and each clinical score (Table4).

Discussion

For the evaluation of RA disease activity in clinical practice, composite measurements, such as DAS28, SDAI, and CDAI, have recently been used [2-4]. However, these evaluations do not include the ankle and foot. The rationale for using 28 joints as the criterion for remission is that PtGA scores may increase in those with lesions in the ankle or foot [15]. Moreover, US-

detected subclinical foot and ankle synovitis affected composite indices, patients, and pain visual analog scale scores [16]. In this study, hand GS and PD scores showed a significant positive correlation with composite measurements and levels of serum inflammatory biomarkers, such as CRP and MMP-3, while no positive correlation was found for foot GS and PD score with any factor, including PtGA and mHAQ scores. Consequently, it is more likely that forefoot US-detected synovitis, excluding the mid- hindfoot, does not influence the global assessment of disease activity and functional statement. In this study, a large gap exists between physical examination and joint US in regard to the detectability of lesions in the forefoot. Accordingly, as physical examination is inadequate to precisely diagnose synovial inflammation in the forefoot, US assessment is useful for detecting synovitis that is difficult to find on physical examination. A study reported that PD has a higher intraclass correlation (ICC) than GS [17] and becomes a predictor of radiographic progression [18]. PD can better visualize active synovitis, which causes joint destruction, with higher accuracy and reproducibility than physical examination and GS-US. In this study, PD and GS showed approximately equivalent results; however, a thickened synovial membrane is frequently found at the first and second MTP joints, even in healthy subjects [19]. A certain number of PD-negative GS-positive cases were also detected in this study, but not all of them may be pathological. Thus, evaluation by GS may lead to the overestimation of the arthritis disease stage in the forefoot, making PD desirable for accurate evaluation of pathological synovial inflammation. Another study reported on the progression of joint destruction with persistent PD signal, even if the patient has achieved clinical remission [20]; therefore, for latent synovitis detectable on PD, intensified therapy may be considered.

The results of this study were limited by the small sample size and cross-sectional design. Longitudinal studies are needed to investigate the effect of ultrasound-detected synovitis on joint destruction. In addition, NSAIDs were used in $\geq 80\%$ of the patients, which reduced pain due to synovitis in the forefoot, thus resulting in lower PtGA scores.

In conclusion, our data confirm that forefoot synovitis detected by US is not reflected in the composite measures of disease activity and patient-reported functional ability. To detect even minimal asymptomatic synovial lesion of the forefoot in patients with RA, including subclinical synovitis, direct ultrasound assessment may be useful.

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Conflict of interest statement

None.

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