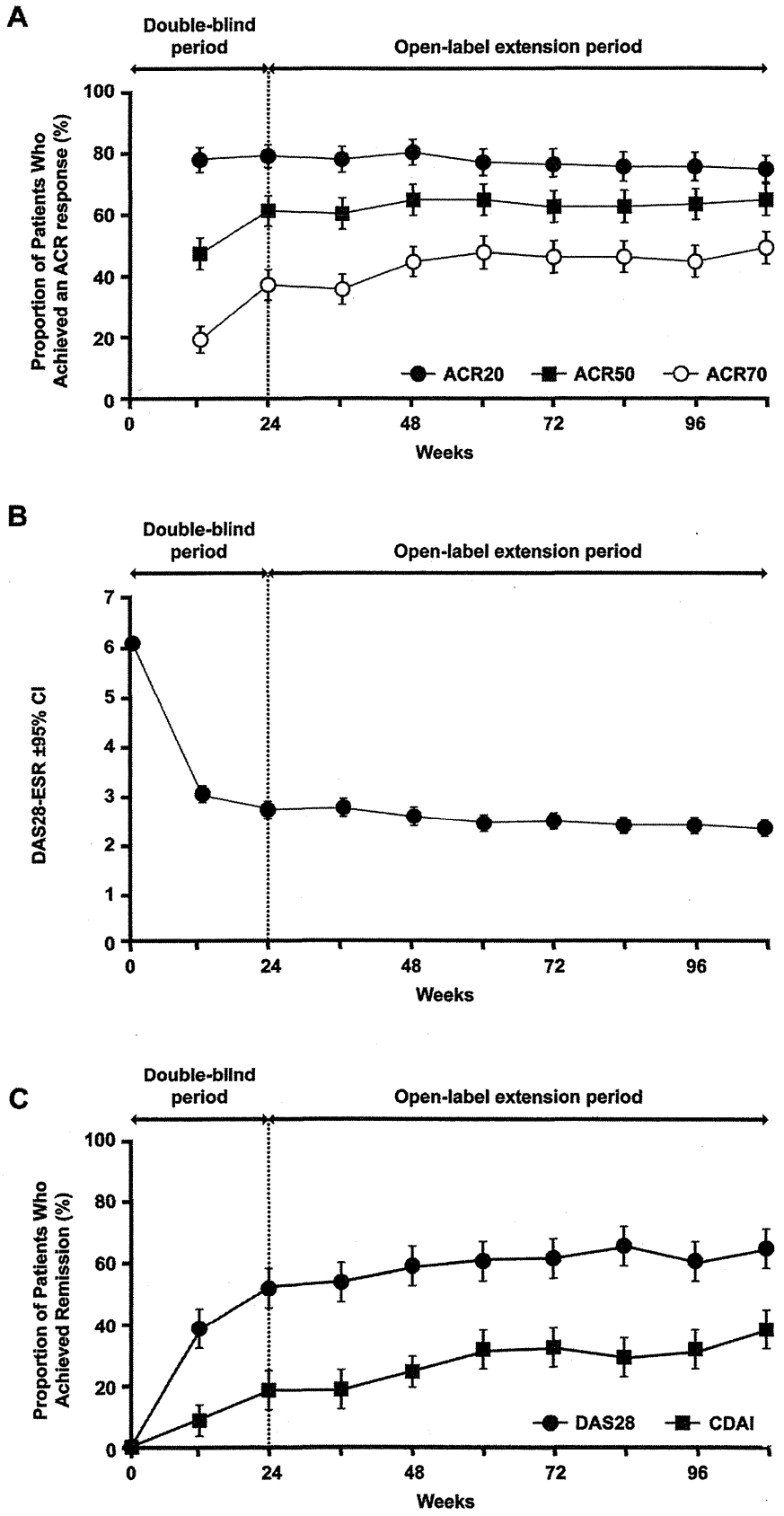

Figure 4. Maintenance of clinical response during longterm treatment with subcutaneous tocilizumab monotherapy. A. Proportions of patients who achieved an American College of Rheumatology (ACR) response rate of 20% (ACR20), 50% (ACR50), and 70% (ACR70). B. Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR). C. Proportions of patients who achieved clinical remission [DAS28-ESR < 2.6 and Clinical Disease Activity Index (CDAI) ≤ 2.8]. For missing data, nonresponder imputation was applied to response data (ACR20/50/70), DAS28 remission, and CDAI remission, while last observation carried forward was applied to continuous data (DAS28). Data are presented with 95% CI. Both double-blind (Day 1 to Week 24) and longterm extension (weeks 24–108) data are presented.

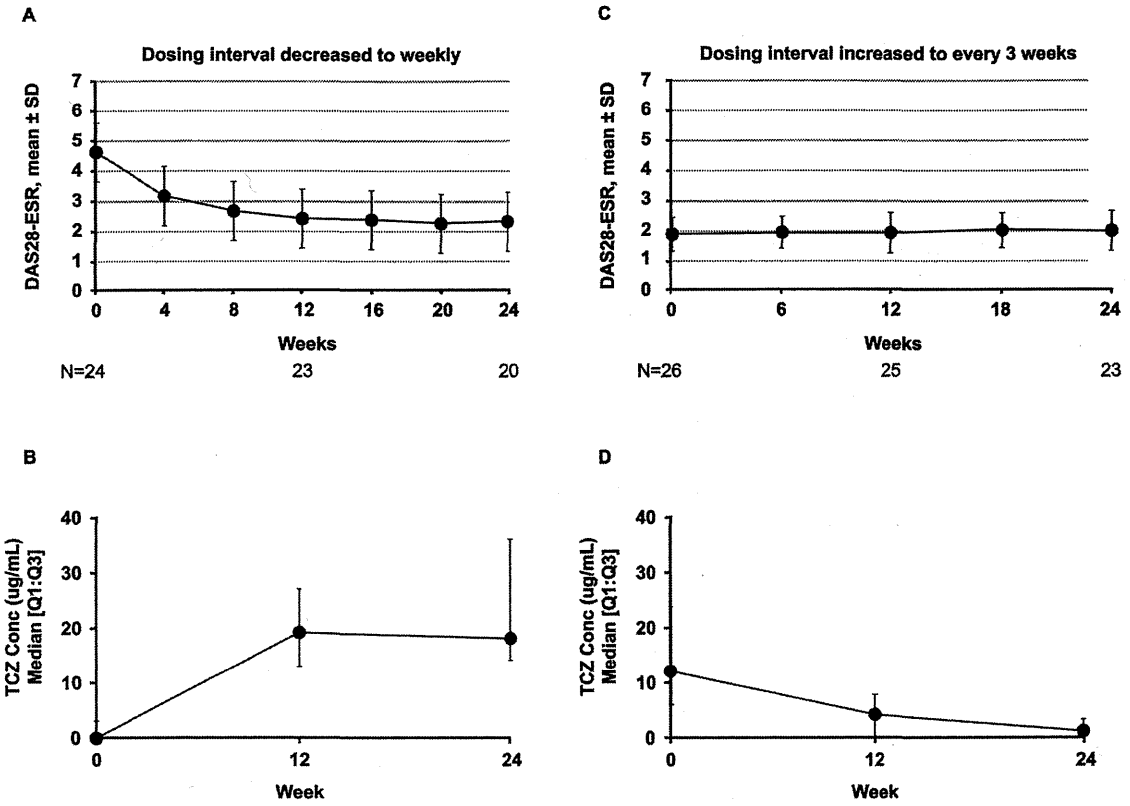

Figure 5. Mean 28-joint Disease Activity Score (DAS28-ESR) and the serum concentration (Conc) of tocilizumab (TCZ) observed after changing the dosing interval to weekly (panels A, B) in inadequate response to subcutaneous TCZ monotherapy every 2 weeks (TCZ-SC-mono q2w) or every 3 weeks (panels C, D) after achieving remission by TCZ-SC-mono q2w. Reasons for the patients' withdrawal from interval shortening were adverse event (n = 1), low efficacy (n = 1), and other (n = 2). DAS28 are expressed as mean ± SD and TCZ concentrations are expressed as the median with the first and third quartile. ESR: erythrocyte sedimentation rate.

TCZ-SC-mono qw. After the dosing interval was decreased from TCZ-SC-mono q2w to qw, the proportion of patients with AE with increased triglycerides or ALT or decreased platelets or neutrophils did not increase.

DISCUSSION

The OLE period of the MUSASHI study evaluated the longterm safety and efficacy of TCZ-SC-mono 162 mg q2w in Japanese patients with RA. These results confirmed our original findings at 24 weeks and demonstrated that TCZ-SC-mono provided a sustained favorable safety and efficacy profile. The safety profile of TCZ-SC-mono was observed in previous studies of TCZ-IV and was associated with a risk/benefit ratio that supports its use in patients with RA[14,19,20]. The proportions of patients who achieved an ACR20/50/70 response, low disease activity (DAS28-ESR ≤ 3.2), or remission (DAS28-ESR < 2.6) at Week 24 were maintained over the 108 weeks. Retention rates were similar to those seen in longterm studies of TCZ-IV[19,20].

The longterm safety profile of TCZ-SC-mono was determined during the 108 weeks of our study. The treatment was generally well tolerated, and the associated AE profile was consistent with the known and well-established safety profile of TCZ. Although the short-term safety profiles of TCZ-SC-mono and TCZ-IV-mono were similar, there is no direct comparison of the longterm safety profiles of TCZ-SC-mono and TCZ-IV-mono. Because half the patients received TCZ-IV-mono for 24 weeks and then switched to TCZ-SC-mono for 84 weeks, we can only indirectly compare the longterm safety of TCZ-SC-mono and TCZ-IV-mono. In comparing the TCZ-SC-mono data from our study to the cumulative safety data from TCZ-IV phase III trials[20], we saw no additional concerns about TCZ-SC-mono. Future direct comparison of longterm safety of TCZ-SC-mono and TCZ-IV-mono will be necessary.

Maintenance of longterm efficacy is a key consideration in the management of RA. From Week 24 to Week 108, there was a gradual increase in the proportion of patients who achieved an ACR20/50/70 response, an improvement of category in ACR response, and a clinical response as evaluated by DAS28-ESR. Overall, after 108 weeks of exposure, there was no attenuation of the therapeutic

response. In our study, the efficacy of TCZ-SC-mono was analyzed by nonresponder imputation or LOCF method because most patients had discontinued owing to an insufficient therapeutic response. However, fewer than 5% of patients discontinued because of an insufficient response. No clinical intolerance during longterm administration of TCZ-SC-mono was observed.

We evaluated adjustment of the administration interval of TCZ-SC in various situations in a limited number of patients (open-label setting). Previous studies had demonstrated that maintenance of serum trough concentration of TCZ is important for sufficient maintenance of efficacy[18]. Shortening of the administration interval (qw administration of TCZ-SC) was evaluated in patients with inadequate response to TCZ-SC-mono q2w. Shortening of the TCZ-SC-mono q2w dosing interval to qw improved DAS28-ESR and increased the proportion of patients who achieved clinical remission. In most of these patients, TCZ-SC-mono qw enhanced the efficacy with an increased serum TCZ concentration, suggesting that inadequate clinical response was due to insufficient maintenance of serum TCZ concentrations, and that shortening the dosing interval to qw would be an effective solution for patients who still have high disease activity after receiving TCZ-SC-mono q2w. Extension of the administration interval (q3w administration of TCZ-SC) was evaluated in patients who achieved clinical remission by TCZ-SC-mono q2w. In these patients, TCZ-SC-mono q3w maintained efficacy without CRP elevation for ≥ 6 months. These results suggest that extension of the administration interval may be possible in good responders to TCZ. Further studies will help validate the results that were shown in this small patient population.

The reasons for insufficient response to TCZ-SC have not been thoroughly elucidated. The main cause seems to be lower serum concentration of TCZ. Because TCZ-SC-mono was administered as a single dose regardless of body weight, low efficacy may have occurred in patients with higher body weight and/or with higher BMI; they received a relatively lower dosage. As previously reported for the MUSASHI study, the TCZ mean serum trough concentrations were lower in patients with high BMI, and the effectiveness of TCZ-SC-mono may be lower in patients with high BMI[16]. In other reports about patients with RA, a high BMI has been associated with decreased clinical responses to treatments including biologics[21,22,23]. In addition, the BREVACTA study[24] evaluated the effectiveness of a biweekly dosing interval for TCZ-SC combined with MTX, as stratified by body weight. Those results[16,24] suggested that shortening of the TCZ-SC treatment interval may be a good option to improve disease activity in patients with higher body weight. Future studies will be necessary to uncover the reasons for the insufficient response to TCZ-SC-mono, effect of dosing interval shortening, and the relation to the serum trough concentration, because our present study was small.

In 23 of 26 patients who achieved remission, efficacy was maintained after extension of the injection interval (q3w). Although the concentration of TCZ was decreased, the small amount of TCZ may have been enough to neutralize IL-6 function in patients who achieved remission because IL-6 production was decreased. The concentration of TCZ was decreased from 12 weeks after the interval extension through 36 weeks (data not shown). Therefore, some patients for whom the dosing interval is changed to q3w may need to return to the q2w dosing interval.

A limitation of this study is that the design had a double-blind period with patients receiving TCZ-IV-mono or TCZ-SC-mono followed by an OLE period of patients only receiving TCZ-SC-mono. Therefore, in half of patients who were enrolled from TCZ-IV after 24 weeks, the safety and efficacy of TCZ-SC-mono were not assessed for the entire 108 weeks. However, there were no differences in the efficacy and safety between TCZ-IV-mono and TCZ-SC-mono at Week 24[16] in the double-blind period, nor any differences in efficacy and safety between TCZ-IV-mono and TCZ-SC- mono at Week 108 in our study. Additional longterm data from studies with TCZ-SC-mono will confirm the efficacy and safety observed in our study and will provide further information about the longterm risk/benefit ratio.

The safety and efficacy results of this 108-week longterm extension study in Japanese patients with RA are consistent with those in previously published 24-week TCZ-SC-mono studies. It was determined that TCZ-SC-mono demonstrated a favorable risk benefit profile in this cohort of patients because it was well tolerated and the therapeutic responses over time were not attenuated.

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APPENDIX.

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ORIGINAL ARTICLE

Sonographic measurements of low-echoic synovial area in the dorsal aspect of metatarsophalangeal joints in healthy subjects

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Abstract

Introduction. Assessment of synovitis in the metatarsophalangeal (MTP) joints with ultrasound has been shown to improve the accuracy of assessment of rheumatoid arthritis (RA). However, the presence of intraarticular low-echoic synovial area (LESA) in the MTP joints in healthy subjects complicates the sonographic assessment of these joints.

Method. Healthy subjects with no arthritic symptoms in their MTP joints were recruited. All subjects completed a questionnaire and underwent physical examination and sonographic assessment. LESAs in the dorsal aspect of all MTP joints were measured in the longitudinal view.

Results. One thousand non-arthritic MTP joints in 100 healthy subjects (female 73, mean age 41.0 years old) were evaluated. Measurable LESAs were identified in all joints assessed. Mean length of LESA in each of the 1st–5th MTP joints was 17.8, 13.9, 11.9, 10.6, and 9.2 mm, respectively, whereas mean thickness was 2.4, 2.4, 1.8, 1.2, and 0.8 mm, respectively. Multivariate linear regression models identified the difference between 1st and 5th MTP joints as the most independently influential factor on the measurement of LESA.

Conclusions. Our data provide the normal reference values for the measurements of LESA in Japanese, which should be taken into consideration when the synovitis in MTP joints is evaluated with ultrasound.

Keywords

Metatarsophalangeal joint, Measurement, Rheumatoid arthritis, Synovitis, Ultrasound

History

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Introduction

The metatarsophalangeal (MTP) joints are frequently involved in patients with rheumatoid arthritis (RA) and their involvement has adverse consequences on the radiographic and functional outcomes [1–5]. Therefore, the assessment of MTP joints has been included in the 2010 American College of Rheumatology (ACR)/European Colleague Against Rheumatism (EULAR) classification criteria [6,7], ACR core set [8], Disease Activity Score (DAS) [9], and modified Sharp scores [10,11]. A number of studies have reported that the widely used 28-joint count [12], which does not include MTP joints, can underestimate the disease activity of RA [5,13–17], suggesting that the assessment of these joints is important in the management of RA. However, the clinical assessment of MTP joints can be unreliable [18], which partially explains the inconsistent results on the association between MTP joints involvement and radiographic progression [5,17].

Musculoskeletal ultrasound directly visualizes the inflammation in synovial tissues and enables more reliable assessment than clinical examination does [18–20]. Ultrasound has also been shown to improve the accuracy of diagnosis [21–25] and the assessment of disease activity of RA [26–31]. Since MTP joints are the joints where discordance between ultrasound and clinical examination frequently occurs [19,32,33], they have been included in many global sonographic assessment systems for RA [34–38].

However, accurate assessment of mild synovitis in the MTP joints is more difficult even with ultrasound as compared to that in the finger joints due to the presence of intraarticular low-echoic synovial area (LESA) in the non-arthritic MTP joints in healthy subjects, possibly causing overestimation. In order to distinguish between normally identified LESA and pathologic synovial hypertrophy, standard reference values for the measurement of LESA are needed. Although Schmidt et al. reported the standard reference values for the thickness of capsular distension in the 1st and 2nd MTP joints [39], those in the lesser toes, where RA-specific pathologies are frequently identified [4,34,35], remain to be determined.

In this study, we measured the LESA of 1,000 non-arthritic MTP joints in 100 healthy subjects to provide standard reference values for each MTP joint and to determine the factors which independently influence the measurements.

Methods

Study subjects

One hundred volunteers who reported neither any current/previous diseases, any previous injuries, nor any current arthritic symptoms were recruited from the staff members working at the Kirishima Medical Center. The study design and procedures were approved by the Ethics Committee of Chiba University and subjects' written informed consent was obtained according to the Declaration of Helsinki.

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Background survey and physical assessment

All subjects completed a questionnaire form for background information including sex, age, height, weight, dominant foot, and sporting activities. Dominant foot was defined as the foot with which the subject usually kicks a ball. Subjects also underwent physical assessment for the presence of hallux valgus, which was determined whether the angle between two lines tangential to the medial aspects of 1st metatarsal and 1st proximal phalanx was $>15°$.

Ultrasound examination

A gray-scale (GS) ultrasound was performed in a temperature-controlled room by a single sonographer (MH), who was experienced in musculoskeletal ultrasound, using a HI VISION Ascendus with a linear array multi-frequency transducer (5–18 MHz for GS) (Hitachi Medical Corporation, Tokyo, Japan). Machine settings were not changed throughout the study period with a B mode gain at 17 dB and a dynamic range of 70 dB.

Dorsal aspect of the 1st to 5th MTP joints were assessed bilaterally. Patients lay on a couch in the supine position, keeping the sole flat on the couch with the ankle and toes relaxed. The knee was flexed to a right angle. Each joint was thoroughly scanned and a longitudinal imaging plane which was perpendicular to the bone surface at midline of the toe was determined. The footprint of transducer was placed approximately parallel to the skin surface above the joint space, where the anisotropy of joint capsule was minimal. LESA was defined as an intraarticular region continuous from joint space, which is recognized on ultrasound as a low-echoic area relative to the surrounding tissues. The length of LESA was defined as the maximum distance between two parallel lines which were tangential to the proximal and distal rims of LESA (Figure 1A), whereas the thickness of LESA was defined as the maximum distance between two parallel lines, one was tangential to the surface of metatarsal covered by LESA and the other was tangential to the superficial rim of LESA (Figure 1B). Measurements were performed on images with a clearly visible layer of gel, which ensured that minimal pressure was applied to the skin surface.

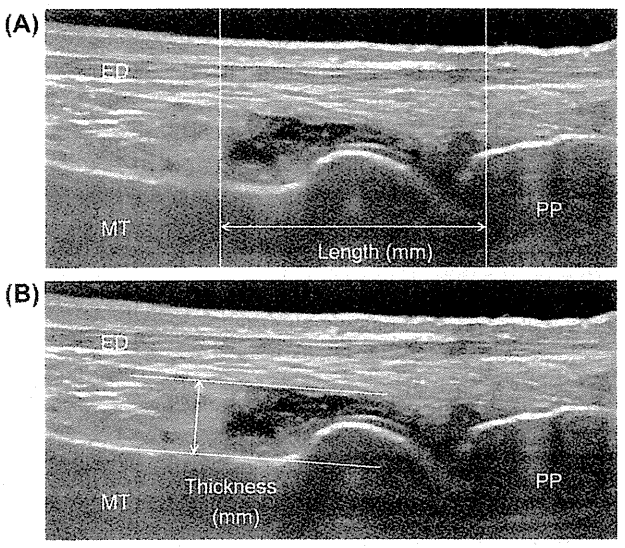

Figure 1. Ultrasonographic measurement of length and thickness of intraarticular low-echoic synovial area in metatarsophalangeal joint. (A) Measurement of length. (B) Measurement of thickness. ED, extensor digitorum; MT, metatarsal; PP, proximal phalanx.

Statistical analysis

Categorical data were summarized with numbers and proportions. Normally distributed continuous data were summarized with means and standard deviations (SDs) and were analyzed using parametric tests (two-sample t-test, paired t-test, or repeated measures ANOVA). Bonferroni's correction was applied for multiple testing. Multivariate analyses were performed using linear regression models with a stepwise method. Statistical analysis was performed using SPSS version 21.0 (IBM Japan, Tokyo, Japan). Two-sided P values less than 0.05 were considered statistically significant.

Results

Study subjects

One hundred healthy subjects free of arthritic symptoms were studied. As shown in Table 1, 73 subjects (73%) were female and mean ± SD age was 41.0 ± 10.2 years old. Mean ± SD height was 159.8 ± 8.5 cm, whereas mean ± SD weight was 55.2 ± 9.4 kg. Ninety-five subjects (95%) reported that their dominant foot was the right one. Seventeen subjects (17%) reported to be currently engaging in some sporting activities. On physical examination, three subjects (3%) had hallux valgus (all female).

Sonographic measurement of intraarticular low-echoic synovial area in 1st–5th MTP joint

A total of 1,000 MTP joints were measured. Measurable LESA was identified in all joints assessed. Mean ± SD length and thickness of LESA in all MTP joints were 12.7 ± 3.6 mm and 1.7 ± 1.0 mm, respectively.

Mean ± SD length of LESA in each of the 1st–5th MTP joints (200 joints each) was 17.8 ± 3.1, 13.9 ± 2.0, 11.9 ± 1.8, 10.6 ± 1.5, and 9.2 ± 1.3 mm, respectively (Figure 2A). There was a statistically significant difference in the length of LESA among 1st–5th MTP joints ($P<0.001$, repeated measures ANOVA) and the differences between any adjacent MTP joints were statistically significant (all $P<0.001$, paired t-test with Bonferroni's correction) (Figure 2A). On the other hand, mean ± SD thickness of LESA in each of the 1st–5th MTP joints was 2.4 ± 1.0, 2.4 ± 0.9, 1.8 ± 0.9, 1.2 ± 0.5, and 0.8 ± 0.2 mm, respectively (Figure 2B). There was a statistically significant difference in the length of LESA among 1st–5th MTP joints ($P<0.001$, repeated measures ANOVA) and the differences between 2nd and 3rd, 3rd and 4th, and 4th and 5th MTP joints were statistically significant (all $P<0.001$, paired t-test with Bonferroni's correction) (Figure 2B).

Comparisons of measurements of low-echoic synovial area between dominant and non-dominant feet

The length and thickness of LESA in all MTP joints were significantly larger in dominant foot (500 joints) than in non-dominant foot (500 joints) (mean ± SD length 12.9 ± 3.8 mm vs. 12.5 ± 3.4 mm, $P<0.001$; mean ± SD thickness 1.8 ± 1.0 mm vs. 1.7 ± 1.0 mm, $P=0.005$; paired t-test).

Table 1. Demographics and characteristics of study subjects.

	Sex		
	Female	Male	Total
Number, n	73	27	100
Age, mean ± SD (year-old)	41.0 ± 10.2	37.7 ± 12.1	42.2 ± 9.3
Height (cm)	156.0 ± 4.9	170.0 ± 7.6	159.8 ± 8.5
Weight (kg)	51.6 ± 6.4	65.0 ± 9.4	55.2 ± 9.4
Sporting activity, present, n (%)	9 (12)	8 (30)	17 (17)
Hallux valgus, present, n (%)	3 (4)	0 (0)	3 (3)

SD standard deviation.

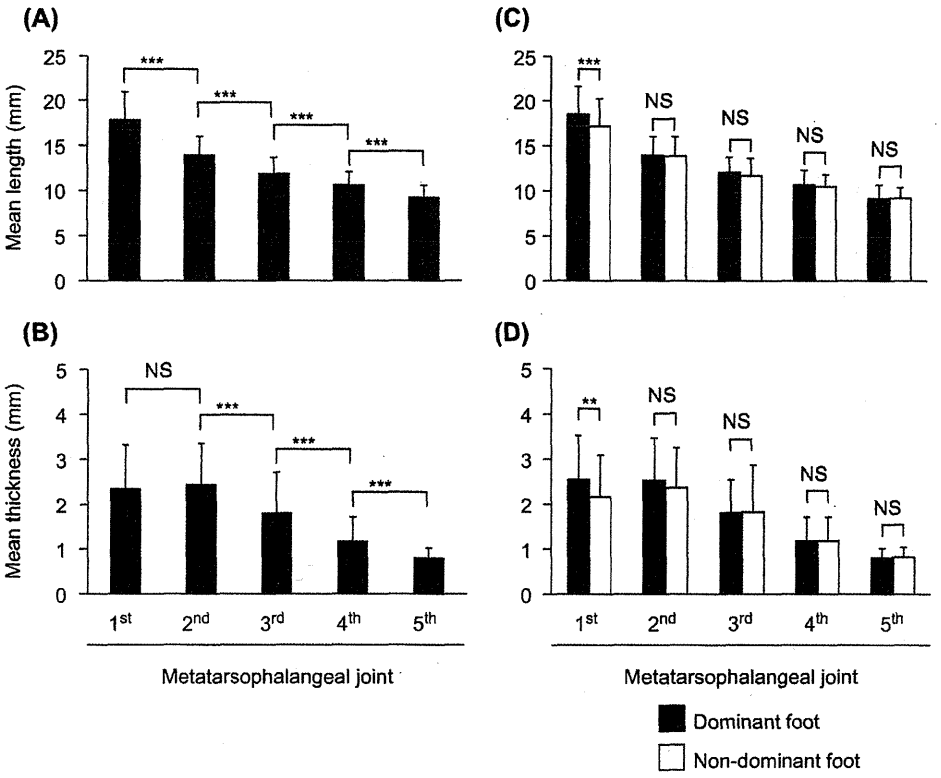

Figure 2. Comparisons of measurements of low-echoic synovial area between 1st and 5th metatarsophalangeal joints and between dominant and non-dominant feet. Presented in bar charts are mean length (A and C) and mean thickness (B and D). Error bars represent standard deviations (SDs). (A and B) Comparisons between different metatarsophalangeal joints. Statistically significant difference was present among 1st–5th metatarsophalangeal joints ($P<0.001$, repeated measures ANOVA). (C and D) Comparisons between dominant (gray bar) and non-dominant (blank bar) feet. *$P<0.05$, **$P<0.01$, ***$P<0.001$, post-hoc test (A and B) or paired t-test (C and D) with Bonferroni's correction. NS, not significant.

When compared in each MTP joint, however, these statistically significant differences were only present in the 1st MTP joint (mean ± SD length 18.5 ± 3.1 vs. 17.2 ± 3.0 mm, $P<0.001$; mean ± SD thickness 2.5 ± 1.0 vs. 2.2 ± 0.9 mm, $P=0.002$) but not in the other MTP joints (paired t-test with Bonferroni's correction) (Figure 2C and D).

Comparisons of measurements of low-echoic synovial area between sexes

The length and thickness of LESA in all MTP joints were significantly larger in male subjects (270 joints) than in female ones (730 joints) (mean ± SD length 13.1 ± 3.6 vs. 12.6 ± 3.6 mm, $P=0.049$; mean ± SD thickness 1.9 ± 1.2 vs. 1.7 ± 0.9 mm, $P<0.001$; two-sample t-test).

When compared in each MTP joint, however, these statistically significant differences were absent except for the length of LESA in the 4th MTP joint (mean ± SD length 11.2 ± 1.5 vs. 10.4 ± 1.4 mm, $P=0.002$, two-sample t-test with Bonferroni's correction) (Figure 3A and B).

Influence of sporting activities on measurements of low-echoic synovial area

The length and thickness of LESA in all MTP joints were significantly larger in subjects who were engaging in sporting activities (170 joints) than in those who were not (830 joints) (mean ± SD length 13.4 ± 3.7 vs. 12.6 vs. 3.6 mm, $P=0.007$; mean ± SD thickness 1.9 ± 1.2 vs. 1.7 ± 0.9 mm, $P<0.001$; two-sample t-test).

When compared in each MTP joint, these statistically significant differences were present in the 1st MTP joint (mean ± SD thickness 2.9 ± 1.2 vs. 2.2 ± 0.9 mm, $P=0.001$), the 2nd MTP joint (mean ± SD length 14.9 ± 2.3 vs. 13.7 ± 1.9 mm, $P=0.017$; mean ± SD thickness 3.0 ± 1.2 vs. 2.3 ± 0.8 mm, $P<0.001$), and the 4th MTP joint (mean ± SD length 11.3 ± 1.6 vs. 10.5 ± 1.4 mm, $P=0.008$; mean ± SD thickness 1.4 ± 0.7 vs. 1.1 ± 0.5 mm, $P=0.032$) (two-sample t-test with Bonferroni's correction) (Figure 3C and D).

Influence of hallux valgus on measurements of low-echoic synovial area

As the proportion of subjects who had hallux valgus was very small, there were no statistically significant differences in the length and thickness of LESA in all MTP joints between subjects who had hallux valgus (30 joints) and those who did not (970 joints) (mean ± SD length 12.7 ± 4.0 vs. 12.7 ± 3.6 mm, $P=0.995$; mean ± SD thickness 1.7 ± 1.0 vs. 1.7 ± 1.0 mm, $P=0.797$; two-sample t-test). The differences were also not statistically significant in the 1st MTP joint or the other MTP joints (two-sample t-test with Bonferroni's correction).

Correlations between age and measurements of low-echoic synovial area

There were no statistically significant correlations between subject's age and the length or thickness of LESA in all MTP joints (length, $r=-0.01$, $P=0.919$; thickness, $r=-0.03$, $P=0.321$; Pearson's correlation coefficient).

When analyzed in each MTP joint, however, weak but statistically significant inverse correlation was present between age and the thickness of LESA in the 5th MTP joint ($r=-0.21$, $P=0.014$, Pearson's correlation coefficient with Bonferroni's correction) (Figure 4).

Correlations between physical frame and measurements of low-echoic synovial area

As expected, weak but statistically significant correlations were present between subject's height and length of LESA ($r=0.10$, $P=0.002$), between height and thickness ($r=0.15$, $P<0.001$), between weight and length ($r=0.08$, $P=0.014$), and between weight and thickness ($r=0.18$, $P<0.001$) (Pearson's correlation coefficient).

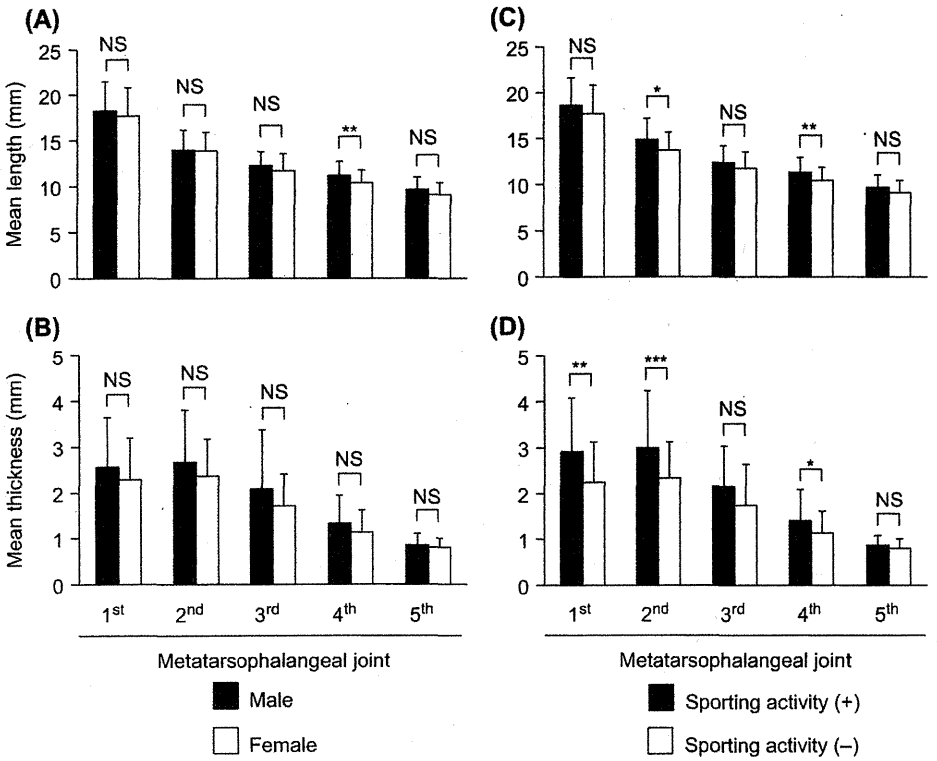

Figure 3. Comparisons of measurements of low-echoic synovial area between sexes and between presence and absence of sporting activities. Presented in bar charts are mean length (A and C) and mean thickness (B and D). Error bars represent standard deviations (SDs). (A and B) Comparisons between male (gray bar) and female (blank bar). (C and D) Comparisons between presence (gray bar) and absence (blank bar) of sporting activities. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, two-sample *t*-test with Bonferroni's correction. NS, not significant.

When analyzed in each MTP joint, statistically significant correlations were present between height and length in the 2nd MTP joint ($r=0.19$, $P=0.043$), the 3rd MTP joint ($r=0.22$, $P=0.008$), the 4th MTP joint ($r=0.29$, $P<0.001$), and the 5th MTP joint ($r=0.27$, $P<0.001$) (Figure 5A); between height and thickness in the 2nd MTP joint ($r=0.26$, $P<0.001$), the 3rd MTP joint ($r=0.26$, $P=0.001$), and the 4th MTP joint ($r=0.27$, $P<0.001$) (Figure 5B); between weight and length in the 4th MTP joint ($r=0.20$, $P=0.019$) and the 5th MTP joint ($r=0.28$, $P<0.001$) (Figure 5C); and between weight and thickness in the 1st MTP joint ($r=0.24$, $P=0.024$), the 2nd MTP joint ($r=0.32$, $P<0.001$), the 3rd MTP joint ($r=0.25$, $P=0.002$), and the 4th MTP joint ($r=0.27$, $P<0.001$) (Figure 5D).

Multivariate linear regression models

Multivariate linear regression analyses were performed to identify the factors which independently influenced the length and thickness of LESA in all MTP joints ($n=1{,}000$). As shown in Table 2, how close to the 1st MTP joint was the single dominant

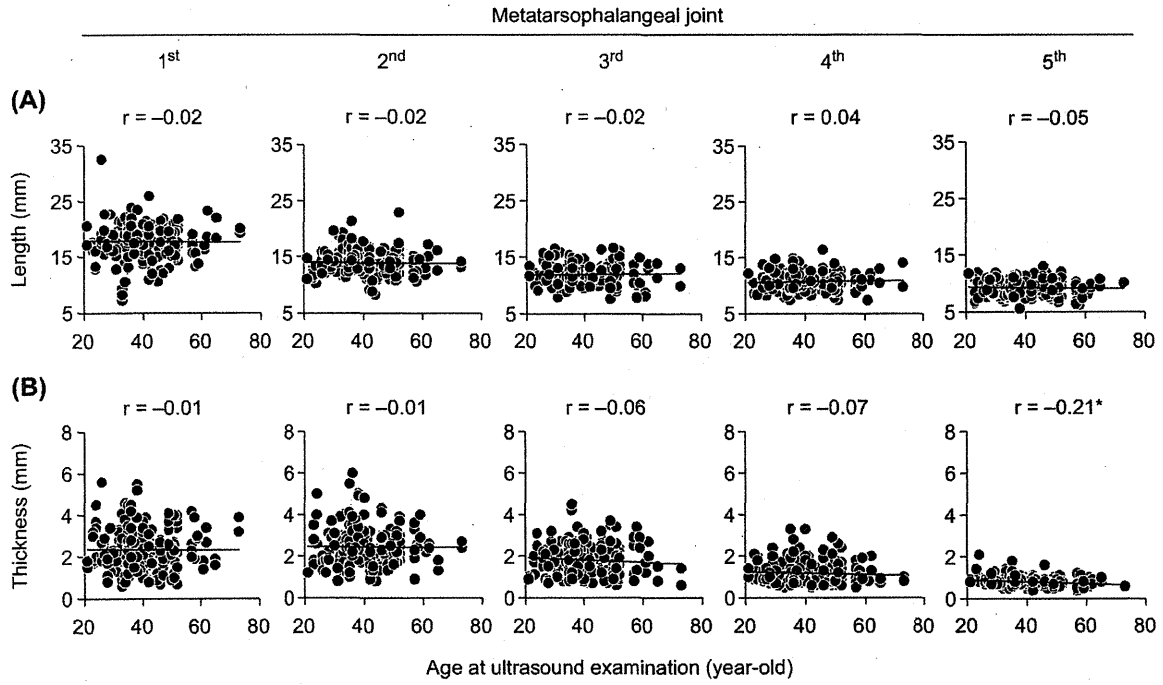

Figure 4. Correlations between age and measurements of low-echoic synovial area. (A) Correlations between age and length. (B) Correlations between age and thickness. Presented above each scatter plot is Pearson's correlation coefficient (*r*). $^{*}P<0.05$.

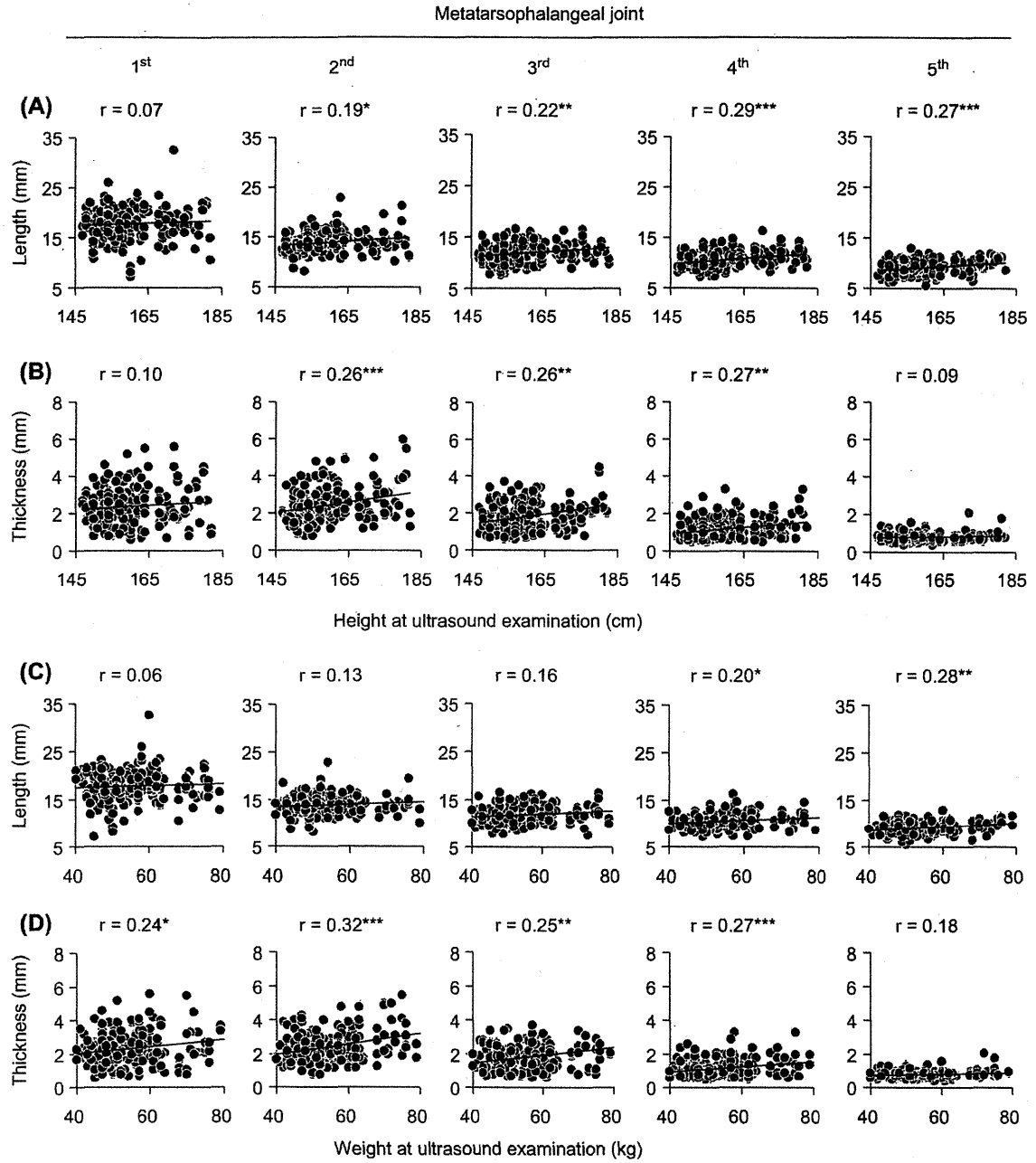

Figure 5. Correlations between physical frame and measurements of low-echoic synovial area (A) Correlations between height and length. (B) Correlations between height and thickness. (C) Correlations between weight and length. (D) Correlations between weight and thickness. Presented above each scatter plot is Pearson's correlation coefficient (r). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

factor for both the length (β coefficient −0.798, $P<0.001$) and the thickness (β coefficient −0.622, $P<0.001$) of LESA. Whether engaging in sporting activities or not and whether in the dominant foot or not were a slightly but significantly influential factor on both the length (sporting activity, β coefficient 0.065, $P=0.001$; dominant foot, β coefficient 0.051, $P=0.006$) and the thickness (sporting activity, β coefficient 0.121, $P<0.001$; dominant foot, β coefficient 0.047, $P=0.048$) of LESA. Interestingly, patient's height significantly influenced only the length (β coefficient 0.082, $P<0.001$), while patient's weight significantly influenced only the thickness (β coefficient 0.155, $P<0.001$).

Discussion

In this study, measurable LESA was identified in all MTP joints assessed, confirming that a normal, non-arthritic MTP joint usually exhibits intraarticular low-echoic area on ultrasound in the dorsal aspect. This finding has a considerable implication on the assessment of synovitis in these joints. Synovial fluid and hypertrophy are defined as "*abnormal* hypoechoic or anechoic-intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal" and "*abnormal* hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal", respectively [40]. Thus, *normal* LESA should be subtracted from the sonographic finding when the presence and the severity of gray-scale synovitis in the MTP joint are assessed, particularly using a certain grading system [41]. Moreover, our data demonstrate that LESA in the 1st and 2nd MTP joints are significantly longer and thicker as compared to those in the lesser MTP joints and the measurements decrease towards the 5th MTP joint. These data indicate that the severity of gray-scale synovitis should not be overestimated in

Table 2. Linear regression models for measurement of low-echoic synovial area in metatarsophalangeal joints of healthy subjects.

Dependent variable	Explanatory variable	β coefficient	*P* value
Length	MTP joint number (1st–5th)	−0.798	<0.001
	Height	0.082	<0.001
	Sporting activity	0.065	0.001
	Dominant foot	0.051	0.006
Thickness	MTP joint number (1st–5th)	−0.622	<0.001
	Weight	0.155	<0.001
	Sporting activity	0.121	<0.001
	Dominant foot	0.047	0.048

MTP metatarsophalangeal.

the 1st and 2nd MTP joints, while the severity should not be underestimated in the MTP joint in lesser toes.

Exact histopathology of LESA in the MTP joints remains unknown. Anechoic fluid that was displaceable and compressible was present in the vast majority of LESAs in the MTP joints. However, hypoechoic intraarticular tissue that was nondisplaceable and poorly compressible was also frequently identified in LESAs (Figure 1) although separately measuring these different sonographic features was technically difficult. Because LESA in normal MTP joints does not usually accompany Doppler signals [42], the non-fluid part of LESA can represent either thickened synovial lining, edematous subintimal tissue, or cellular infiltration without significant vascularization, probably due to the constant mechanical stress in the fore foot.

As compared with the differences between 1st and 5th MTP joints, other factors showed much smaller independent influence on the measurements of LESA in multivariate analyses (Table 2). Nevertheless, it is interesting to note that the subject's height only influenced the length of LESA, whereas the subject's weight only influenced the thickness. The models also retained sporting activity and dominant foot as a significantly influential factor, suggesting that repeated mechanical stress or overuse can result in the subclinical enlargement of LESA in MTP joints.

We had hypothesized that the LESA in MTP joints would be larger in older subjects because previous studies had reported the high prevalence of synovitis in the joints with degenerative changes in the foot [42,43] and the other joints [44–47]; however, age did not significantly influence the measurements of LESA in the multivariate analyses in our study (Table 2) and it inversely correlated with the thickness of LESA in the 5th MTP joints in the univariate analysis (Figure 4B). We assume that the occurrence of degenerative changes that accompany synovial inflammation is infrequent in non-arthritic, relatively young subjects. We also speculate that the inverse correlation between age and the thickness of LESA in the 5th MTP joints in our study was due both to the lighter weight in older subjects ($r = -0.10$, $P = 0.001$, Pearson's correlation coefficient) and to the younger age of subjects who were engaging in sporting activities (mean age 36.9 vs. 41.8 years old, $P = 0.068$, two-sample *t*-test).

This study has several limitations. First, all subjects in our study were Japanese and our data may not be globally generalizable. In fact, mean values for the thickness of synovial area in the 1st and 2nd MTP joints in our study were larger than those in the report by Schmidt et al. [39] even though our study subjects were significantly shorter and lighter. Multinational studies are needed to elucidate whether this is due to differences in the methods of measurements, the machines used, or subjects' life style and genetic background.

Second, synovial Doppler signal was not evaluated in our study. The absence of synovial Doppler signal in the normal MTP joints, which Keen et al. had already reported [42], could have also been confirmed in our study. In addition, comparison with other imaging modalities such as MRI would have added construct validity to our measurements.

Third, the associations between various factors and the measurements of LESA demonstrated in this study can only be applied to the subjects without arthritic symptoms. Technically, whether these associations can also be applied to synovial hypertrophy (i.e. *abnormal* LESA) in symptomatic subjects needs further confirmation.

In conclusion, our data confirm that intraarticular low-echoic synovial area is identified with ultrasound in non-arthritic MTP joints in healthy subjects and also provide the normal reference values in Japanese subjects. Our data also demonstrate that the low-echoic area is larger in the 1st and 2nd MTP joints as compared with that in the lesser MTP joints, which should be taken into consideration when the synovitis in MTP joints is evaluated with ultrasound.

Conflict of interests

None.

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The OMERACT Ultrasound Working Group 10 Years On: Update at OMERACT 12

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ABSTRACT. Musculoskeletal ultrasound (US) now thrives as an established imaging modality for the investigation and management of chronic inflammatory arthritis. We summarize here results of the Outcome Measures in Rheumatology (OMERACT) US working group (WG) projects of the last 2 years. These results were reported at the OMERACT 12 meeting at the plenary session and discussed during breakout sessions. Topics included standardization of US use in rheumatic disease over the last decade and its contribution to understanding musculoskeletal diseases. This is the first update report of WG activities in validating US as an outcome measure in musculoskeletal inflammatory and degenerative diseases, including pediatric arthritis, since the OMERACT 11 meeting. (J Rheumatol First Release March 15 2015; doi:10.3899/jrheum.141462)

Key Indexing Terms:
JOINT EROSIONS OUTCOME ASSESSMENT ULTRASONOGRAPHY

As of 2015, musculoskeletal ultrasound (US) can no longer be considered as controversial in rheumatology; on the contrary, US thrives as an established imaging modality for the investigation and management of chronic inflammatory arthritis. Last year marked the 10-year jubilee of the OMERACT US working group (WG). Members of the WG met in Budapest, Hungary, for the OMERACT 12 conference, where results of the last 2 years of ongoing projects were presented. The several milestones reached in standardizing the use of US in rheumatic disease over the last decade and the contribution of US to understanding musculoskeletal diseases were highlighted in the plenary session and discussed during breakout sessions. This report provides an update on the activities of the WG in validating US as an outcome measure in musculoskeletal inflammatory and degenerative diseases including pediatric arthritis, since the last report on WG activities at OMERACT 11[1].

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A Decade Put into Historical Perspective

At OMERACT 7 in 2004, a special interest group (SIG) dedicated to US was formed by a group of international rheumatologists with the aim of exploring the metric properties of musculoskeletal US. At this early stage, a systematic review of the musculoskeletal US literature in rheumatoid arthritis (RA)[2] dissected the various gaps in existing knowledge, particularly underscoring the lack of US definitions of rheumatic pathology, instrument reliability, and instrument validity. Overall agreement was that because research resources of the SIG were limited, efforts had to be strictly prioritized. The very first publication of the group reported on a core set of practical US definitions for general rheumatic manifestations including synovitis, tenosynovitis, and erosions[3]. In considering which strategy to use, iterative exercises on synovitis in patients with RA were carried out from 2004 to 2010. These exercises involved US assessment of synovitis at both the patient level and the joint level[4,5,6,7]. It was not surprising that the intra- and interexaminer κ values for reading still images were better than for those of real-time image acquisition[8].

By 2008, the perspective of developing an US disease activity score based on synovitis at the patient level loomed as a logical next step, i.e., a global synovitis score (GLOSS). Development of a GLOSS was the result of an iterative, gradual, slow-moving process, implicating a step-by-step approach that included several issues, e.g., the optimal number of joints, how to scan these (dorsal, volar), and B-mode alone or in combination with power Doppler. On the basis of favorable results of the preceding exercises[4,5,6,7], an US-GLOSS, combining B-mode synovial hypertrophy and power Doppler in 1 score, was presented at OMERACT 10[8]. An additional advantage is that the GLOSS can be performed *à la carte*, i.e., in various joint number configurations. Subsequently, responsiveness of the GLOSS was tested in an international multicenter open-label medication trial evaluating responsiveness of power Doppler US in patients with RA with incomplete clinical response to methotrexate and treated with abatacept[9]. Preliminary results were reported at OMERACT 11[10]. During the group discussions and feedback sessions, a need for separate development of diagnostic and monitoring RA GLOSS systems was expressed. Currently, questions need to be addressed on which US findings are preferred for establishing a definite diagnosis (i.e., discrimination findings), and which findings are preferred for monitoring purposes, or for predicting/evaluating remission or flare for that matter. In addition, it is not yet clear how frequently US scans have to be repeated[11]. Two ongoing trials are assessing some of these aspects, namely, the TURA study (NTC 02056184), which is a longitudinal international randomized controlled trial (RCT) targeting remission, and the REVECHO study (NCT02140229), which is a longitudinal international RCT targeting the best strategy for maintaining longstanding remission.

As mentioned in the preceding report of OMERACT 11, testing the metric properties of US on tenosynovitis and tendon damage in patients with RA was another prioritized research area[12,13,14,15]. From a clinical point of view, tendon damage may be an important endpoint in RCT; it would also be clinically relevant to understand which US findings at joint and tendon level are able to predict tendon damage. Results of the tendon damage study in patients with RA showed good to excellent κ values for intraobserver and interobserver reliability[14]. Additionally, an atlas of US images on tenosynovitis and tendon damage in RA was published as online material[15].

Current Research Agenda. "True Erosion," Gout, Pediatric Arthritis, OA, and Dactylitis

During the workshop, the ongoing research agenda focused on additional data including the validation of US in RA erosions and in pediatric arthritis, as well as on new development of US as an outcome measure for other inflammatory rheumatic diseases, such as psoriatic arthritis (PsA) and gout. These topics were first presented in the plenary introduction and then discussed in the breakout sessions.

The first topic focused on the validation of US for detecting RA bone erosions. S. Finzel presented new findings on the prevalence of erosions versus normal cortical "breaks" in patients with RA and healthy controls, using high-resolution peripheral quantitative computed tomography as the gold standard. The rationale of these studies is to get a better idea of what a "true US erosion" represents. Subsequently, the intraobserver and interobserver reliability of US detecting these structures was tested in patients with RA and healthy controls by 12 rheumatologists expert in US (Table 1). Based on the outcome of this study, further studies are planned to define an US-detected RA erosion and the minimal size that can be accurately detected.

Next, a presentation by L. Terslev provided insights into how US can assess the 3 key domains in gout, i.e., inflammation, damage, and urate load[16]. By using a previous systematic literature review, 4 elementary US components were identified, i.e., double contour sign, aggregates, tophi, and erosion[17]. The US definitions of these 4 identified lesions were agreed upon by the group using a Delphi exercise[18]. Subsequently, the metric properties of these components were

Table 1. US testing intraobserver and interobserver reliability on small erosions in patients with RA and healthy controls.

	Intraobserver		Interobserver	
	Normal Break	Abnormal Break	Normal Break	Abnormal Break
Palmar long	0.1–0.8	0.6–0.9	0.8	0.9
Dorsal long	0.4–0.6	–0.1–0.5	0.4	0.7
Palmar transv	0.2–0.7	0.5–0.7	0.7	0.5
Dorsal transv	0.3–0.9	0.4–0.8	0.3	0.4

US: ultrasound; RA: rheumatoid arthritis.

assessed in a patient reliability study conducted in Berlin, December 2013. Preliminary results were presented, showing acceptable intraobserver reliability for detecting and acquiring images of double contour, tophi, and erosions, but not for aggregates. Interobserver κ values were even lower[16]. On the basis of the reliability results, overall agreement was that further validation was needed for double contour sign and aggregates.

A. Iagnocco presented work conducted in hand osteoarthritis (OA). Results of a reliability study focusing on cartilage damage showed intrarater and interrater κ of 0.52 and 0.80 using dichotomous scoring[19]. A second reliability exercise was aimed at evaluating the possibility to grade together structural damage in hand OA, by using a semiquantitative grading of both cartilage and osteophyte lesions. This study showed good results for osteophyte scoring, but moderate for cartilage[20]. Overall agreement was that an US core domain set to be used in hand OA structural lesions should include cartilage scoring in a dichotomous way and osteophyte scoring on a semiquantitative scale (0–3).

J. Roth presented the latest concepts of how US can be used as an instrument for assessment of pediatric pathology. A core domain set for pediatric pathology has yet to be determined. The US definitions of joints of healthy children have recently been published[21]. The next step is to define synovitis in children with juvenile idiopathic arthritis (JIA), which shall be done by consensus through consecutive Delphi rounds. The main objective of the pediatric Delphi process is to obtain consensus on the B-mode and Doppler US elementary components to include in the definition of synovitis in children. The secondary objective is to obtain consensus on the type of scoring system that will be developed. Both the synovitis definition and the scoring system will subsequently be tested in future US exercises in children with JIA.

The last topic was dactylitis, presented by G. Kaeley. He explained that dactylitis was identified as part of a domain core set for PsA. US candidate elementary components have been identified through a literature review[22]. A Delphi process is under way to reach consensus on the initial set of elements that warrant study. Based on the results of the first round, the candidate elements were prioritized (Figure 1). A second round of the Delphi process is being conducted to plan a reliability exercise looking at evaluating the identified elementary lesions.

Following these presentations, each subgroup was divided into smaller discussion groups (about 15 participants each, including 2 patient partners), who were then asked to consider a set of 4 draft questions based on endorsement of the work done and the future research agenda of the group by OMERACT participants (Table 2). Draft questions pertained to construct validity of hand OA, a core domain set of US to be used in gout patients, a core domain set to be used in patients with PsA, and lastly, future research in RA erosions. Each discussion group then reported its main points to all participants at the end of the breakout sessions.

Following this report, the questions were voted on for

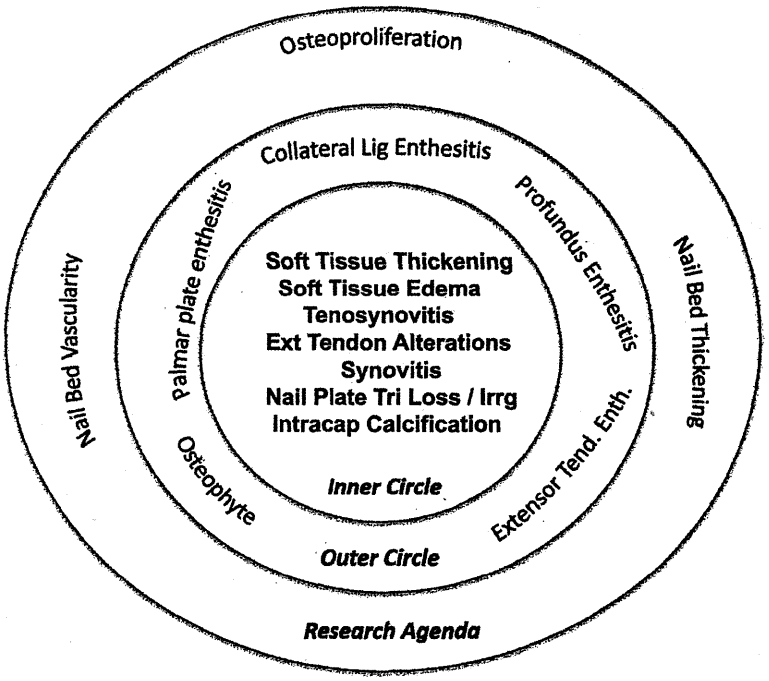

Figure 1. Categorization of candidate elements in dactylitis into domains after first round of Delphi process. Nail plate Tri Loss / Irrg: loss of nail plate trilaminar structure and/or irregularity of nail plate; Intracap calcification: intracapsular calcification; Lig: ligament; Tend.: tendon; Enth.: enthesitis.

Table 2. Endorsement of 4 voting questions in the final plenary session.

Voting Question	Endorsement, %
Do you agree to investigate the correlation between structural damage and inflammation and clinical outcomes in hand OA?	81
Do you agree that US can be developed as an outcome instrument in dactylitis?	77
Do you agree that an ultrasound domain core set in gout should include urate load, inflammation, and damage?	76
Following successful work on synovitis and tenosynovitis in RA, should we continue to work on erosions?	76

OA: osteoarthritis; US: ultrasound: RA: rheumatoid arthritis.

potential endorsement by all conference participants at the final plenary session on the last day of the conference. The topics proposed in the formulated questions were endorsed by a strong majority of attendees.

Below, the main points of discussion are reported. Regarding the US detection of erosions, there was widespread recognition of the importance of developing an US validated measure of erosions, since this tool is widely introduced in the evaluation of RA synovitis. Participants agreed that the evaluation of erosions by US would provide valuable support for early detection of erosive disease. In addition, the higher sensitivity of US for detecting erosions compared to radiography, owing to its better resolution and to the tomographic nature of the technique, is considered an added value. The detection of erosions in early inflammatory disease was felt to be a priority research area and an objective to be tested in future clinical trials. However, additional validation was required before proposing US as a standard outcome measurement of structural damage. For example, more data on the discriminative capability of US for distinguishing between normal cortical breaks and small erosions is needed. One breakout group pointed out the need for additional RCT supporting the responsiveness of inflammatory findings, such as synovitis, before moving to structural damage. Nevertheless, general agreement was expressed on the potential interest of this tool in evaluating erosions.

There was also strong agreement that US is a valuable tool for evaluation of patients with gout. Based on discussions in the breakout groups, several key points were raised by participants, especially as related to the role of US in gout. The importance of US in evaluating urate load was underscored. Participants agreed on the valuable role of US in distinguishing and measuring acute and chronic gout and in identifying core domains for both stages of disease (tophi, synovial inflammation, aggregates, and urate deposits). However, there remains a lack of clear definitions of elementary lesions detected by US. Therefore, discussions were mostly related to which lesions should be assessed by US and which definitions should be used. The discriminative ability of US gout lesions in comparison to other arthropathies has been suggested as a priority for validation.

The third question, based on the development of US in PsA, also received agreement from the majority of participants. In each breakout group in which this topic was discussed, unanimous concordance on the need to pursue standardization of US for management of PsA was reached. The value of US in the evaluation of PSA synovitis was recognized and supported, as well as the potential value of US in the evaluation of dactylitis. The development of US as a responsive tool for following this clinical manifestation was unanimously supported. Finally, the potential development of a structural US score in hand OA was discussed. On the basis of the work already performed by the WG in terms of inflammatory abnormalities, agreement was obtained that the future research agenda should focus on correlations between structural and inflammatory lesions and clinical outcomes in symptomatic hand OA.

The objectives of this workshop were to present both the existing knowledge on the use of US in areas that have been explored over the last decade and to decide priorities for future research. US is a unique outcome measure that reveals both the past and present status of various rheumatic diseases. Considerable progress has been reported in different areas, including synovitis and structural damage in RA, tenosynovitis in RA, and structural damage in hand OA. At this stage it is not possible to predict the influence of the workshop's success in these areas, but the effects may be far-reaching, both for daily practice and clinical research. Examples of the aspect of daily practice may be other treatment expectations or less use of radiographic radiation; an example of the clinical research aspect may be novel insights into pathogenetic mechanisms, e.g., in OA.

Here follows the research agenda drafted to address existing gaps in our knowledge regarding work to be done in hand OA, gout, PsA, and erosions (Table 3):

- To investigate the construct validity of US assessment of hand OA as compared to clinical manifestations of the disease
- To assess the metric properties of US in other OA joints (e.g., the knee)
- To further define the basic abnormalities evaluable with US in gout and to test the reliability, responsiveness, and discriminant capacity of these lesions
- To further identify and define the basic US abnormalities that can be included in the US assessment of PsA and to test their metric properties
- To further address the concurrent validity and sensitivity to change of US-detected early bone erosions
- To develop definitions for joint inflammatory pathology in childhood

Other areas of future research include systemic vasculitis, synovial biopsy, and knee OA. Over the next 2 years, fresh data will be reported on the different topics of the research agenda.

Table 3. Future research agenda and time line of the OMERACT US working group.

US Research Field	Outcome	Research Phase
Detection of minimal erosions in RA	Minimal erosion	Validity studies
Definition of an US core domain set in gout	Inflammation, damage, urate load	Delphi study on definitions/reliability
Definition of an US core domain set in hand OA	Structural lesions	Delphi study/reliability
Definition of an US core domain set in PsA	Dactylitis	Delphi study
Definition of an US core domain set in pediatric arthritis	Synovitis	Delphi study on normal sonoanatomy and synovitis

US: ultrasonography; RA: rheumatoid arthritis; OA: osteoarthritis; PsA: psoriatic arthritis.

APPENDIX

List of study collaborators: OMERACT Ultrasound Task Force: Philippe Aegerter, Sibel Aydin, Marina Backhaus, David Bong, Isabelle Chary-Valckenaere, Paz Collado, Eugenio De Miguel, Christian Dejaco, Oscar Epis, Jane E. Freeston, Frederique Gandjbakhch, Walter Grassi, Petra Hanova, Sandrine Jousse-Joulin, Fredrick Joshua, Juhani Koski, Damien Loeuille, Ingrid Möller, Viviana Ravagnani, Anthony Reginato, Veronica Sharp, Nanno Swen, Marcin Szkudlarek, Richard J. Wakefield, and Hans-Rudolf Ziswiler.

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Predicting joint destruction in rheumatoid arthritis with power Doppler, anti-citrullinated peptide antibody, and joint swelling

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ORIGINAL ARTICLE

Predicting joint destruction in rheumatoid arthritis with power Doppler, anti-citrullinated peptide antibody, and joint swelling

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Abstract

Objective. To determine combined evaluation of musculoskeletal ultrasonography (MSUS) and power Doppler (PD) signals, anti-citrullinated peptide antibody (ACPA), and other clinical findings improve the prediction of joint destruction in rheumatoid arthritis (RA).

Methods. We performed a retrospective study of 331 RA patients (female $n = 280$ and male $n = 51$, mean age: 57.9 ± 13.2 years) who underwent MSUS from 2002 to 2012. Correlations with progression of joint destructions in 1,308 2nd and 3rd metacarpophalangeal (MCP) joints and various factors including PD signals of the same joints, clinical findings, age, disease duration at the study entry, gender, observation period, radiographic bone scores according to modified Sharp–van der Heijde methods, ACPA, and rheumatoid factor (RF) were analyzed in patient- and joint-based fashions, using univariate and multivariate logistic regression analyses and generalized linear mixed model.

Results. Patients' characteristics were as follows: mean disease duration: 5.7 ± 7.5 years, observation period: 4.6 ± 2.6 years, RF positivity: 79.9%, and ACPA positivity: 77.5%. PD-positive 2nd and 3rd joints showed higher rate of joint destruction, especially in ACPA-positive patients. Moreover, PD-positive joints in ACPA-positive patients showed joint destruction even in joints without swelling. Multivariate analysis determined PD, swollen joint (SJ), observation period, basal radiographic bone scores, and ACPA as independent risks for joint destruction.

Conclusion. PD, SJ, basal radiographic bone scores, and ACPA are independent predictors for the joint destruction of 2nd and 3rd MCPs in RA; thus, considering these factors would be useful in daily practice.

Keywords

Power Doppler, Prediction, Ultrasound

History

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Introduction

Implementation of the 2010 Rheumatoid Arthritis Classification Criteria has highlighted the importance of early intervention of the disease [1,2]. Along with early diagnosis and the treat-to-target concept, "hit hard and early" treatment strategy has been successfully integrated in the practice [3]. However, intensive treatments could also lead to overtreatment and significant side effects [4]. It would be of great benefit if patients who are expected to be rapid radiological progressors (RRP) requiring intensive treatment are identified in advance. Power Doppler (PD) signals in musculoskeletal ultrasonography (MSUS) is a promising mean to predict future joint damage [5–7], but it is usually not included in the models for the prediction of radiographic progression [8–10].

MSUS, becoming a common modality for evaluating joint inflammation in rheumatoid arthritis (RA), has now been applied for various clinical settings such as diagnosis of early RA [11] and evaluation of remission [12–15]. Japanese rheumatologists introducing the techniques in daily clinic are rapidly increasing [7]. Our institute has accumulated the data of MSUS-based RA evaluation since 2002. We reported the use of MSUS for the assessment of disease activity even in RA patients receiving tocilizumab which potently suppresses C-reactive protein or CRP and erythrocyte sedimentation rate or ESR as components of established composite measurements for disease activity such as Disease Activity Score in 28 Joints or DAS28 [16]. Our study comparing PD signals with pathological findings confirmed that intensity of PD highly correlated with the extent of synovium vascularity in RA, but not in osteoarthritis (OA) [17]. Moreover, we showed that PD signals were associated with joint destruction even in RA patients in clinical remission [13]. These papers reinforced the notion that PD is tightly connected to joint destruction in RA. Indeed, several lines of evidence suggest that PD signals predict radiographic joint destruction [5,18], but these studies involved relatively small

On behalf of Y-CURD study group.

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number of patients in short observation period, therefore may be underpowered to detect other factors influencing the link between PD signals and joint destruction. Since radiological remission, in which structural damages are completely suppressed, is recognized as one of the therapeutic goals of RA, it is important to identify RRP who need early intensive therapy [19].

In the current study of RA, association between PD scores and 2nd and 3rd metacarpophalangeal (MCP) joints destruction in 331 patients who underwent MSUS for the evaluation of RA disease activity in daily clinic was retrospectively analyzed, which is one of the largest sample size for MSUS study to the best of our knowledge. Among the variants that we considered, PD signal was the strongest risks for joint damage in RA. The study also raised the possibility of predicting joints at high risk of destruction in combination with PD, presence of swollen joints (SJs), and anti-citrullinated peptide antibody (ACPA).

Methods

Five hundred and sixty-five RA patients who underwent MSUS from June 2002 to December 2012 at Yokohama City University Hospital, Yokohama, Japan, were enrolled in this retrospective study. The inclusion criteria was that the patients should have taken bilateral hand X-ray (Xp) in independent occasions at an interval of more than 1 year. All of the patients were of self-reported Japanese ethnicity, and fulfilled the American Rheumatism Association 1987 revised criteria for the classification of RA [20]. These patients underwent MSUS for evaluating RA disease activity in daily clinic. Gender; age; Steinbrocker stage; disease duration at the time of MSUS; presence of SJ, ACPA, and rheumatoid factor (RF) positivity; and treatments with or without methotrexate (MTX) and/or biologics during the follow-up period were also included in the analysis.

MSUS

MSUS was performed by experienced physicians who were blinded to evaluation of Xp scores of the study (Y.K., H.M., K.T.M., Y. Kunishita, D.K., R.Y., and Y.A.). PD signals at the bilateral 2nd and 3rd MCP joints were evaluated semi-quantitatively (score: 0–3) as described previously [16]. Score 0 was defined as negative, whereas scores 1–3 were positive. The joints were scanned longitudinally and transversally from the dorsal view. Bilateral 2nd and 3rd MCP joints were selected for this study because those joints have been analyzed consistently since 2002, they exhibit the highest PD positivity among MCP joints [21,22], and have been included in OMERACT ultrasound task force study [23]. Inter-observer reliability for PD score using the Cohen's kappa was "excellent" with a value of 0.91 in our facility [16]. The ultrasound devices employed in the study were Toshiba Aplio SSA-700A from year 2002 to 2008, and Toshiba Viamo thereafter, equipped with a 12-MHz linear array transducer. Among patients who underwent MSUS for several times, the oldest MSUS data of each patient, whose hand Xp taken within the 6-month interval with MSUS was available, were used for the analysis.

Evaluation of Xp findings

Baseline bilateral hand Xp taken within 6 months before or after the date of MSUS, and the latest Xp were compared (Y.K.). In case Xp were taken several times, ones having the shortest intervals with MSUS date were selected. The time intervals between these Xp were defined as follow-up period, which was more than 1 year in all patients. For the radiographic assessment of 2nd and 3rd MCP joints according to modified Sharp–van der Heijde scoring system by a physician blinded to the US findings during the analysis [24]. Joint space narrowing (score: 0–4) and bone erosion (score: 0–5) were evaluated in each joint (maximal score of 9). Sum of these radiographic bone scores in 4 MCP joints were defined as "SUMBS," and included in patient-based analysis. For the patient-based analysis, sum of PD scores (SUMPD) on 4 joints (bilateral 2nd and 3rd MCP joints, maximal score of 12) and yearly progressions of the same joints (maximal score of 36) were evaluated. In this study, "joint destruction" was defined as positive interval change of the score of the 4 joints. Yearly progression was calculated by dividing the change of joint score during the observation period by follow-up period.

Statistical analysis

SPSS version 19 (IBM Japan, Tokyo, Japan) and GraphPad Prism (San Diego, CA, USA) were used for the analysis. Unpaired Welch's *t*-test, one-way analysis of variance or ANOVA, and Tukey's correction for multiple comparisons were applied. For the cumulative probability plot, we applied Mann–Whitney *U* test. To estimate the relative risk, joint destruction was converted into binary state and the chi-square test was applied. Logistic regression models were used to quantify the effect of characteristics on progression in the patient-based analysis. For joint-based analysis, a generalized linear mixed model with random intercept was used because data were clustered within patients. The variables found to be significant in univariate analysis were included in the following multivariate analysis. Age and sex were forcedly entered in the multivariate analysis.

Results

Characteristics of the RA patients

Among 565 patients who underwent MSUS during 2002–2012, we excluded 41.4% of patients because hand Xp or MSUS datasets were unavailable for the analysis, which retained 311 patients in the study. Characteristics of the patients at the time of study entry are summarized in Table 1. Mean age, percentage of female, and ACPA and RF positivity were similar with large-scale Japanese RA cohort IORRA [25]. As expected, disease duration was significantly correlated with Steinbrocker stage, supporting the validity of these variables (data not shown). Mean follow-up period of the study was 5.7 ± 7.5 years. During the follow-up period, 74.6% and 38.1% of the patients were treated with MTX and/or biologics, respectively, which were significantly more than those in IORRA

Table 1. Baseline characteristic of RA patients analyzed in the study.

	Current study	IORRA [25,26]
Age (range)	57.9 ± 13.2 (20.7–87.8)	59
Gender *n* (%)		
Female	280 (84.6)	(85.1)
Male	51 (15.4)	
Disease duration at MSUS (range)	5.7 ± 7.5 years (–4.9–38.5)	
Follow-up after MSUS (range)	4.6 ± 2.6 years (1–10.7)	
Steinbrocker stage *n* (%)		
I	143 (43.2)	
II	66 (19.9)	
III	35 (10.6)	
IV	87 (26.3)	
Auto-antibodies *n* (%)		
ACPA +	158 (77.5)	(84.2)
RF +	263 (79.9)	(74.1)
Treatments *n* (%)		
MTX	247 (74.6)	(68.5)
Biologics	126 (38.1)	(8.7)

MSUS, musculoskeletal ultrasonography; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; MTX, methotrexate.
Data are shown in mean ± standard deviation.