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FULL PAPER

Composite assessment of power Doppler ultrasonography and MRI in rheumatoid arthritis: a pilot study of predictive value in radiographic progression after one year

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Objective: Power Doppler ultrasonography (PDUS) and MRI are independently useful to predict structural damage in patients with rheumatoid arthritis (RA). We hypothesize that there is a complementary relationship between these modalities. The aim of this study is, therefore, to investigate the usefulness of the predictive value of composite assessment of PDUS and contrast-enhanced MRI in radiographic outcomes in patients with RA.

Methods: 20 patients (17 females and 3 males) with RA on disease-modifying antirheumatic drugs underwent PDUS and MRI of both hands at baseline. Radiography of the bilateral hands was performed at baseline and at 1 year. Articular synovitis on PDUS was evaluated according to quantitative measurement. Synovitis, bone marrow edema and bone erosion were scored according to the RA MRI scoring method. The changes of joint space narrowing and bone erosion on radiograph were assessed by the Sharp/van der Heijde method. We applied t-statistics to combine the assessment of quantitative PDUS with semiquantitative MRI.

Results: Structural damage progression for radiography was not correlated with any evaluations for MRI, while it showed significant correlation with synovitis on PDUS (r_s = 0.597, p = 0.005). The composite assessment of both modalities (synovitis for PDUS and bone marrow edema for MRI) was correlated with structural damage progression on radiograph (r_s = 0.792, p < 0.0001).

Conclusion: Composite assessment of PDUS and MRI may have a stronger predictive value in radiographic progression than PDUS or MRI alone in RA.

Advances in knowledge: Composite assessment of PDUS and MRI may be an effective predictor of structural damage in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which frequently leads to progressive joint destruction.[1–3] The progression of structural damage in RA can be assessed by radiography and is associated with the development of joint deformity and eventually with disability.[4,5] Along with recent advances in RA treatment, early diagnosis has also become possible, which enables accurate prognostication for structural destruction. Ultrasonography and MRI are currently used for this purpose.[6–8]

Power Doppler ultrasonography (PDUS) can capture inflammatory changes of synovial proliferation of joints, tendon sheaths, bursae, and increased blood flow associated with synovial proliferation. Proliferative synovitis is

the earliest pathologic abnormality in RA, and is also responsible for bone and cartilage damage.[7] With disease progression, neovessels are seen within the thickened (first hyperplastic and then hypertrophied) synovium.[8]

For MRI evaluation, the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (RAMRIS) is currently the gold-standard. It consists of semiquantitative assessing of synovitis, bone marrow edema (BME), and bone erosion and is sensitive to change over weeks as well as months.[9,10] MRI is the only imaging technique that can visualize BME, which is a lesion within the trabecular bone, having ill-defined margins and signal characteristics consistent with increased water content and may occur alone or surrounding an erosion or other bone abnormalities.[11] In a histological study of bone from patients with RA, McQueen et al suggest that a cellular infiltrate comprising lymphocytes and osteoclasts may be detected in subchondral bone and could mediate the development of erosions from the marrow towards the joint surface.[12]

There are a number of studies assessing imaging biomarkers in relation to progression of RA. Naredo et al report that PDUS inflammatory findings seem to have a predictive value in disease activity as well as radiographic outcome during 1 year of follow up ($r = 0.59–0.66$, $p < 0.001$).[13] Some researches indicate a quantitative PDUS method was more useful than a semiquantitative method.[14–16] Fukae et al[14] suggest that the quantitative value for power Doppler signal is predictive of structural damage progression during the 20th week. MRI synovitis and BME at baseline has also been shown to be an independent predictor of radiographic damage.[17]

We hypothesize that there is complementary relationship between PDUS and MRI in terms of joint damage prediction. To the best of our knowledge, there are no papers which quantitatively combine findings of PDUS and MRI for the progression of structural destruction in RA. The aim of the current study is to investigate the usefulness of the predictive value of composite assessment of PDUS and MRI in radiographic outcome after 1 year in patients with RA.

METHODS AND MATERIALS

Patients

The study population comprised of 20 (17 females, 3 males) patients with active RA on disease-modifying antirheumatic drugs (DMARDs) (Table 1). The inclusion criteria were RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[18] All patients were managed in a dedicated rheumatology ward in a university hospital and were assessed for continuation/cessation of the biological treatment or for switching to an alternative biological agent. They were recruited from consecutive patients admitted to the university hospital. They underwent PDUS and MRI of the bilateral hands with an average of 4 day interval at baseline. Radiography of the bilateral hands was performed at baseline and at 1 year with a median of 13 months. Out of 20 patients, 19 already received DMARDs for RA at baseline of this study. One patient, thereafter, underwent DMARDs. This study was approved by the local ethics committee of our institution (Hokkaido University Hospital) and was performed in accordance with the Declaration of Helsinki. Informed consent was waivered because of the retrospective study design.

Table 1. Clinical and laboratory characteristics of patients with RA at baseline

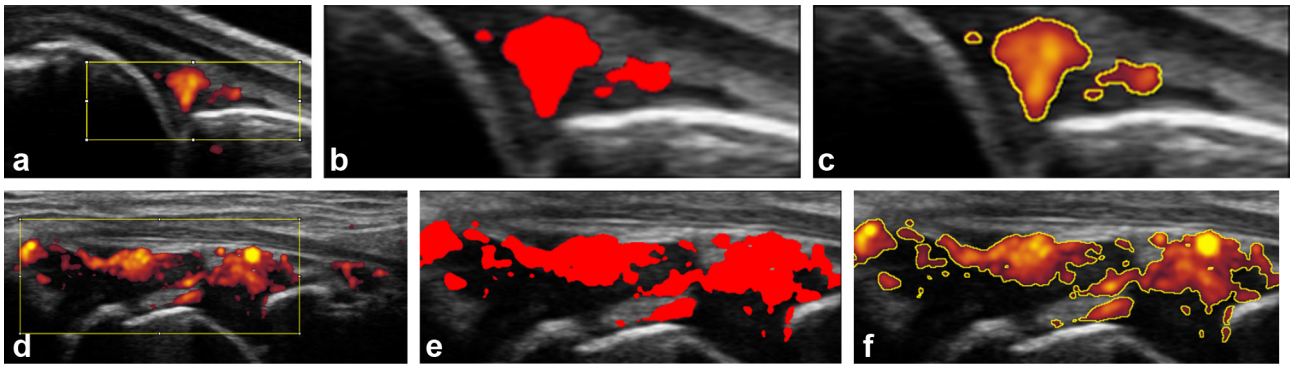
Characteristic	Value
Total no. of subjects included	20
Age, mean (range) years	60 (34–75)
Sex, female/male	17/3
RF positive, yes/no	17/3
Duration of symptoms, median (IQR) years, $n = 20$	2.5 (1.4–6.3)
Swollen joint count, median (IQR), $n = 20$	4 (1–9)
Tender joint count, median (IQR), $n = 20$	5 (1–9)
VAS, median (IQR), $n = 20$	34 (17–60)
ESR, median (IQR) mm h^{-1}, $n = 20$	18 (8–42)
CRP, median (IQR) mg dl^{-1}, $n = 20$	0.26 (0.03–0.69)
DAS-ESR, median (SD), $n = 20$	4.5 (2.8–5.3)
DAS-CRP, median (SD), $n = 19$	3.7 (2.3–4.6)
RF, median (IQR), $n = 19$	31 (8–113)
CCP, median (IQR) IU ml^{-1}, $n = 19$	80 (7–300)
MMP3, median (IQR) ng ml^{-1}, $n = 19$	70 (32–115)
HAQ, median (IQR), $n = 18$	5 (1–8)
Prior use of DMARDs, yes/no	19/1
DMARDs, no.	
None	1
Methotrexate	8
Tocilizumab	1
Combine therapy	10

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, interquartile range; MMP3, matrix metalloproteinase-3; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; VAS, visual analog scale.

PDUS and assessment

All ultrasonography examinations were performed using an Avius (Hitachi Aloka, Tokyo, Japan) or LOGIQ E9 (GE Healthcare, Piscataway, NJ) by ultrasonographers specialized in musculoskeletal ultrasonography who were blinded to other clinical information. For Avius, using a linear probe 6–14 MHz, pulse repetition frequency (PRF) 800 Hz at preset were adjusted: FINGER; depth, 1.75 cm; color focus, 1 cm; Doppler gain, 40; color flow mapping filter, M; transmit power, 1.0; frame rate, 8–10. For LOGIQ E9, using a linear probe, ML6-15, PRF 500 Hz at preset were adjusted: MSK superficial; depth, 2.75 cm; color focus, 1.5 cm; Doppler gain, 15; transmit power, 0.4; frame rate, 10. For both models, the level of wall filter was automatically determined according to PRF settings by linked controls.

Figure 1. Representative ultrasound image for quantitative assessment of the metacarpophalangeal joint (a–c) and wrist joint (d–f). (a, d) The ROI was a standardized rectangle [(a) 5 × 15 mm, (d) 10 × 25 mm] that was located to contain as many of the vascular flow pixels as possible. (b, e) Image cropped for yellow rectangle ROI in Figure 1(a, d), respectively. The regions of the vascular flow pixels (red pixels) were distinguished from the other regions by manually setting the optimal threshold in the ImageJ software while referring to the original image. (c, f) The regions corresponding to the vascular flow pixels were automatically surrounded by a free-form curve. The number of pixels with a positive Doppler and that inside the rectangle ROI appear on the screen as area; [(c) 6.65 and 76.50 mm^2, (f) 54.56 and 249.71 mm^2, respectively]. A synovial vascularity value was calculated to be (c) 8.69% (percentage of 6.65/76.50) and (f) 21.85% (percentage of 54.56/249.71), respectively. ROI, region of interest.



The transmit frequencies were 7.5 MHz for Avius and 15 MHz for LOGIQ E9. Pulse Doppler settings were standardized for the detection of synovial blood flow by adjusting color gain, pulse repetition, and flow optimization parameters according to the method in a previous study.[15] The first to fifth metacarpophalangeal, first to fifth proximal interphalangeal joints and the wrists were scanned in the longitudinal plane over the dorsal surface. The basic scanning technique followed the European League Against Rheumatism guidelines.[19]

A synovial vascularity value, measured by quantitative PDUS according to the previous study,[15] is the number of vascular flow pixels in the region of interest (ROI). The ROI was a rectangle 5 × 15 mm for the finger and 10 × 25 mm for the wrist, located to contain as many of the vascular flow pixels as possible. The maximum value obtained from the synovial sites was evaluated in each joint. Vascular flow pixels in the ROI were measured using ImageJ (free software) (Figure 1, online only for colour image). One radiologist with 20 years of experience (TK), who was blinded to other clinical information, determined the location of the center of the ROI for each static PDUS image, followed by ROI placement and quantitative measurement by a fourth year undergraduate student in the radiologic technology course (YS).

MRI and assessment

MR images were acquired with a 1.5 T whole body MRI system (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). Patients were placed on the imaging table headfirst in a supine position. Bilateral hands were positioned on a handmade stand over the pelvis, with the wrist positioned palm downward. The hands were then surrounded with coils (Total Imaging Matrix, Siemens Healthcare). The MRI protocol was implemented using coronal spin echo sequence: repetition time/echo time 682/18 ms; field of view 350 mm; matrix 384 × 384; 15 slices; slice thickness 4 mm; and number of excitations 1. Contrast-enhanced fat-suppressed T_1 weighted images of the hands were obtained after a bolus injection of 0.1 mmol kg^{-1} gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Osaka, Japan) into a vein in the forearm. Note that we used Magnevist before its suspension by the European Medicines Agency on 20July 2017 in its Committee for Medical Products for Human Use as an i.v. contrast medium. The MR scan time for hands was approximately 2 min and 44 s on average.

One radiologist with 20 years of experience (TK), who was blinded to other clinical information, scored synovitis, BME, and bone erosion for the bilateral hands on MR images using RAMRIS with sufficient repeatability demonstrated in previous studies.[20,21] Synovitis was assessed by a score of 0 indicating normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. BME was assessed as follows: 0 = no edema; 1 = 1–33% of bone edematous; 2 = 34–66% of bone edematous; 3 = 67–100%, and the scale for bone erosion was 0–10, based on the proportion of eroded bone compared with the "assessed bone volume": score 0 = no erosion; 1 = 1–10% of bone eroded; 2 = 11–20%, etc.[9] Images after contrast administration are valuable as omitting i.v. contrast injection does not change scores of bone erosions and bone edema, but decreases the reliability of synovitis scores.[22]

Radiography and assessment

All plain radiographs of both hands of the posteroanterior view were acquired using digital X-ray equipment (BENEO DR-XD 100, Fujifilm Corporation, Tokyo, Japan and DHF-155H, Hitachi, Tokyo, Japan) under standardized conditions.

Each radiograph was scored for joint space narrowing (JSN) and bone erosion according to the Sharp/van der Heijde (SvdH) scoring system by one radiologist (TK), who was blinded to other clinical information.[23] Repeatability of scoring is described elsewhere.[24]

Table 2. Descriptive analytical statistics for PDUS, RAMRIS and SvdH scores

	Mean	SD	Median	Range
PDUS (synovitis)	0.58	0.15	0.43	0–2.60
RAMRIS (synovitis)	6.30	1.36	4.00	0–18.00
RAMRIS (BME)	3.05	1.27	0	0–18.00
RAMRIS (bone erosion)	0.95	0.32	0	0–4.00
RAMRIS (total)	10.3	2.41	5.00	0–36.00
SvdH (JSN + bone erosion)_baseline	4.05	1.69	1.00	0–31.00
SvdH (JSN + bone erosion)_follow-up	4.80	1.77	2.00	0–33.00

BME, bone marrow edema; JSN, joint space narrowing; PDUS, power Doppler ultrasonography; RAMRIS, RA MRI scoring system; SD, standard deviation; SvdH, Sharp/van der Heijde score.

Image interpretation for PDUS, MRI, and radiograph was performed by one radiologist with 20 years of experience (TK), who was blinded to other clinical information with more than 1 month interval to avoid memory bias.

Statistical analysis

All statistical analyses were undertaken using Excel (Microsoft Corp., Redmond, WA) and SPSS v.n 22.0 (IBM Corp., New York, NY) for Windows. We applied t-statistics to combine the assessment of quantitative PDUS with semiquantitative MRI. By applying t-statistics, we did not have to consider the difference in the number of joints evaluated according to the gold standard of each modality. Correlations between PDUS, MRI and XR findings were assessed by the Spearman's rank correlation test. Spearman's correlation coefficient was interpreted as follows: $r_s < 0.2$, poor correlation; $r_s = 0.2–0.4$, fair correlation; $r_s = 0.41–0.6$, moderate correlation; $r_s = 0.61–0.8$, good correlation; and $r_s > 0.81$, excellent correlation.[25]

RESULTS

We examined bilateral hands of 20 RA patients on PDUS, MRI and XR. The mean age (range) was 60 (34–75) years and median disease duration was 2.5 [interquartile range (IQR) 1.4–6.3] years. Table 2 shows the assessment of semiquantitative and quantitative methods using PDUS, MRI and XR. The median total SvdH was 1 (IQR 0–4) at baseline. The median total SvdH at the follow-up was 2 (IQR 1–5). There was structural damage progression in 10 patients (as determined by changes in SvdH score). Representative PDUS, MR images and radiographs showing structural damage progression are shown in Figures 2 and 3 (online only for colour image).

Correlations between the assessment of RA on PDUS, MRI and structural damage progression for radiography are shown in Table 3. Structural damage progression for radiography was not correlated with any evaluation of MRI at baseline except for total

Figure 2. Ultrasonography, MRI and radiograph of a 34-year-old male with RA who experienced structural damage progression: (a) power Doppler ultrasonography image at baseline showing synovitis in the right wrist joint. (b) Post-contrast fat-suppressed T_1 weighted image of the right hand at baseline showing synovitis in the radioulnar, radiocarpal and intercarpal–carpometacarpal joints. Bone marrow edema was seen in the capitate, scaphoid and lunate bone. (c) Baseline radiograph of the right hand showing JSN in the SC and RS joints (arrow heads). (d) Radiograph at 1 year follow-up showing stable SC and RS joints (arrow heads). JSN progression in scaphoid–trapezium joint (thin arrow) is demonstrated. JSN, joint space narrowing; RA, rheumatoid arthritis; RS, radius–scaphoid; SC, scaphoid–capitate.

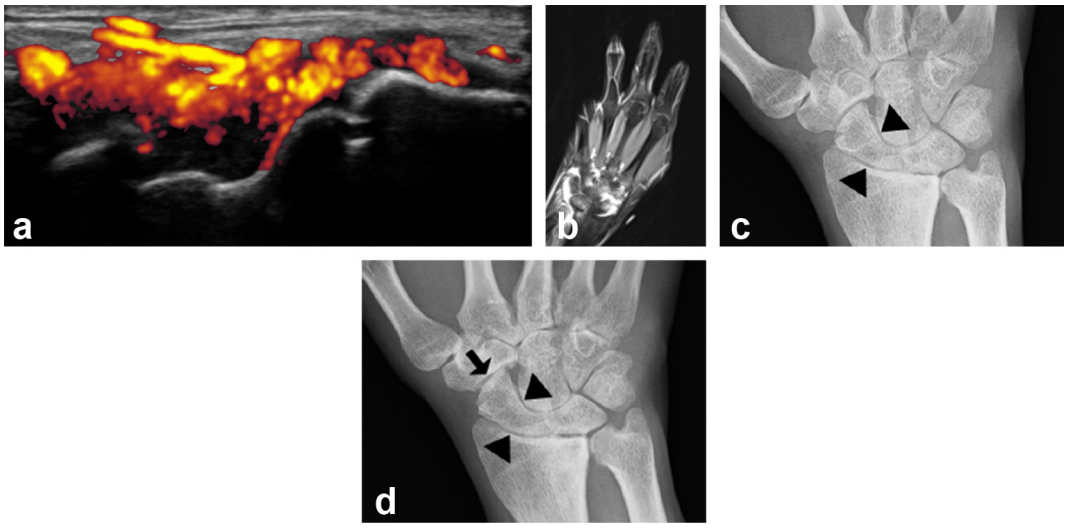
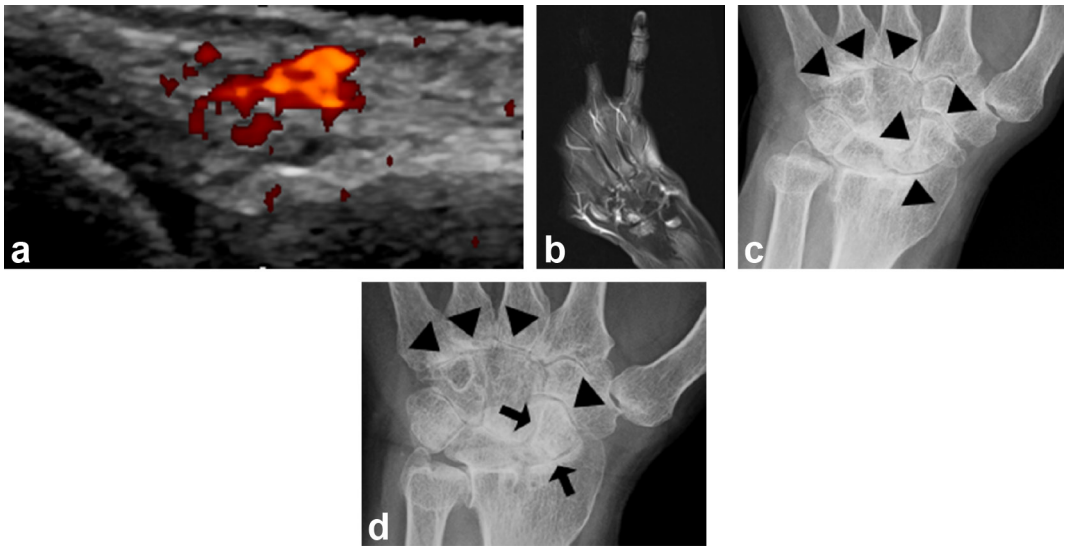


Figure 3. Ultrasonography, MRI and XR of a 60-year-old female suffering from RA with structural damage progression: (a) power Doppler ultrasonography image at baseline showing synovitis in the metacarpophalangeal joint of the right index finger. (b) Post-contrast fat-suppressed T_1weighted image of the left hand at baseline showing synovitis in the radioulnar joint. Bone marrow edema was seen in the scaphoid bone and distal radius. (c) Baseline conventional radiograph of the left hand showing JSN in the third to fifth CM, SC, RS, and ST joints (arrow heads). (d) Conventional radiograph at 1 year follow-up showing stable third to fifth CM and ST joints (arrow heads). JSN progression in SC and RS joints (thin arrows) is demonstrated. CM, carpometacarpal; JSN, joint space narrowing; RA, rheumatoid arthritis; RS, radius–scaphoid; SC, scaphoid–capitates; ST, scaphoid–trapezium.



evaluation of MRI, while it showed significant correlation with synovitis on PDUS at baseline ($r_s = 0.597$, $p = 0.005$).

We next combined the assessment of PDUS with MRI by applying t-statistics and compared with structural damage progression on radiograph (Table 3). The composite assessment of all PDUS with MRI improved the predictive value in radiographic progression. In particular, the composite assessment of both modalities (synovitis for PDUS and BME for MRI) was strongly correlated with structural damage progression on radiograph ($r_s = 0.792$, $p < 0.0001$) (Figure 4).

Table 3. Correlations between MRI or PDUS alone *vs* composite assessment of PDUS/MRI and structural damage on radiograph

	ΔSvdH for radiography
	Correlation coefficient (p-value)
MRI or PDUS alone	
PDUS (synovitis)	0.597* (0.0054)
RAMRIS (synovitis)	0.399 (0.0814)
RAMRIS (BME)	0.392 (0.0871)
RAMRIS (bone erosion)	0.173 (0.4658)
RAMRIS (total)	0.457* (0.0428)
MR data combined with PDUS (synovitis)	
RAMRIS (synovitis)	0.630** (0.0029)
RAMRIS (BME)	0.792** (<0.0001)
RAMRIS (bone erosion)	0.607** (0.0046)
RAMRIS (total)	0.683** (0.0009)

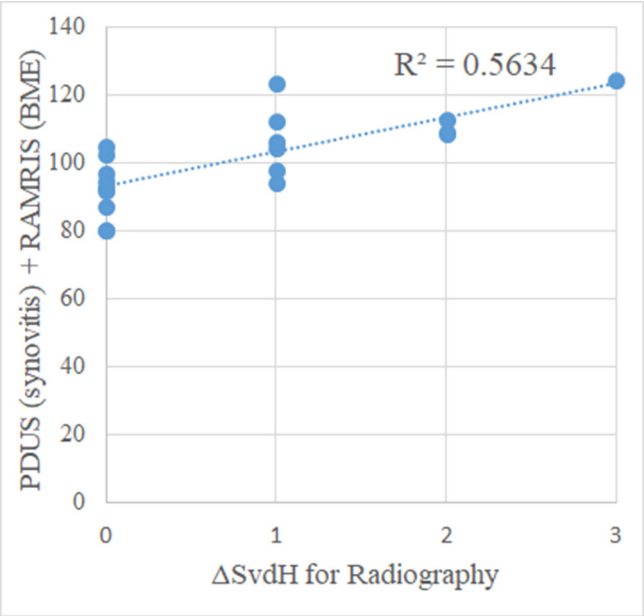
BME, bone marrow edema; PDUS, power Doppler ultrasonography; RAMRIS, RA MRI scoring system; SvdH, Sharp/van der Heijde score.
Asterisks indicate (*) significant correlation (*0.01 < p < 0.05, **p < 0.01).

DISCUSSION

We verified the usefulness of performing both PDUS and contrast-enhanced MRI in active RA patients on DMARDs. The composite assessment of both modalities (synovitis for semiquantitative PDUS and BME for quantitative MRI) was strongly correlated with structural damage progression on radiograph during 1 year follow-up. Several published articles suggest that PDUS and MRI are independently useful to predict structural damage.[6–8,13,14,17,26–29] A recent study showed ultrasound and MRI have an equivalent diagnosis value in synovitis.[30] There seems to be significant association between PDUS and MRI in RA.[31] Moreover, Ogishima et al indicated the qualitative combination of PDUS and MRI was more useful than PDUS or MRI alone for subclinical synovitis and improved the predictive value for bone erosion on radiographs.[29] Our study presents the first supportive evidence on improving the predictive value in radiographic progression after one year by quantitative composite assessment of PDUS and MRI in RA patients.

We combined the assessment of PDUS with MRI by applying t-statistics, which is a standard score. The average of t-statistics is taken as 50 with a standard deviation of 10. Although we could not directly combine the assessment of quantitative PDUS with semiquantitative MRI, by applying t-statistics, we did not have to consider these differences in metrics. When

Figure 4. Correlation between composite assessment of two modalities (synovitis for PDUS and BME for MRI) and structural damage progression on radiograph. Radiographs were scored according to the SvdH scoring system. BME, bone marrow edema; PDUS, power Doppler ultrasonography; RAMRIS, RA MRI scoring system; SvdH, Sharp/van der Heijde, ΔSvdH, progression in the Sharp/van der Heijde score.



assessment of both modalities (synovitis for PDUS and BME for MRI) was combined, there was a better correlation for prediction of structural damage progression on radiograph than MRI and PDUS alone. While both MRI and PDUS can detect synovitis in RA patients, some researchers suggest that ultrasonography is more useful for assessment of synovitis than MRI in terms of prediction of structural damage progression.[28,32,33] Previous studies show that BME of baseline MRI features is a strong, independent predictor of erosive progression.[26,27] These results also show that PDUS is effective for assessment of synovial inflammation and MRI is effective for assessment of bone inflammation. The result of the current study is consistent with these previous studies.[26–28,32,33] Our results indicate that the predictive value in radiographic progression improves by composite evaluation of each modality.

In this study, we evaluated MR data using RAMRIS, a standard semiquantitative MR measure with no significant correlations between the MRI evaluation except for total evaluation of MRI and structural damage progression on radiograph. In a previous study, Hetland et al suggested that MRI BME at baseline is an independent predictor of radiographic damage in 89 patients with early RA during 2 year's follow up (correlation coefficient = 0.75, $p < 0.001$).[26] Furthermore, MRI synovitis has been shown to be associated with subsequent radiographic damage in 55 patients with early RA (Mann–Whitney $p = 0.03$ at 3 year change).[17] Non-significant correlations in our study may be explained by the limited number of patients included. In addition, previous studies consisted of early RA patients and the duration of follow up was longer than 1 year. Numerous quantitative computer-assisted measurement techniques have been shown to be more sensitive than scoring methods (RAMRIS) for MR evaluation.[34–38] Østergaard et al showed that quantitative synovial membrane volume determined by contrast-enhanced MRI correlates with progressive joint destruction assessed by MRI ($r_s = 0.69$, $p < 0.001$), which was superior to visual synovial hypertrophy score ($r_s = 0.44$, $p < 0.05$).[38] MRI findings at baseline might be underestimated by our semi-quantitative two-dimensional MR data due to the retrospective study design.

Numerous researches have established that PD techniques help to promptly detect modifications in synovial vascularity resulting from either the natural history of RA or the response to therapy.[14–16,39,40] In addition, some researches indicate a quantitative PDUS method is more useful than a semiquantitative method for the assessment of synovial vascularity because conventional semiquantitative scoring method consists of only four steps (PDUS score of 0, 1, 2, or 3), which are not able to assess subtle changes with sufficient sensitivity.[15,16] We quantified synovitis on PDUS images in this study according to a previous paper which demonstrated that the quantitative analysis method for synovitis is strongly correlated with visual evaluation and showed almost perfect reproducibility of the method.[15] Inter- and intraobserver reproducibility was, therefore, not assessed in this study.

Limitations to this study must be addressed here. First, only a small number of patients were studied in this retrospective study. Further study is needed to validate a larger patient cohort. Second, MR data acquisition used a relatively large field of view to cover both hands, possibly resulting in decreased spatial resolution compared with parameter settings for a dedicated joint study. This study may, therefore, have underestimated the findings of MR images in terms of responsiveness and prediction of future progression in structural damage during treatment. High-resolution MRI with a dedicated coil will provide a more accurate assessment. Third, intra- and interobserver reproducibility were not assessed in this study. This was because the intraclass correlation coefficient (ICC) value for synovitis, bone-edema, and bone-erosion score of MRI in 30 RA patients by the same expert as this study was in almost perfect agreement (ICC = 0.813) with a previous study, which was performed with the same MR system and parameter settings.[20] Similarly, intra- and interobserver reliability for the SvdH scoring system on radiograph in 51 RA patients by the same expert were moderate to almost perfect in a previous study (ICC = 0.589–0.839 and 0.556–0.849, respectively).[24] Regarding the quantitative PD index, the previous study demonstrated that the interobserver discrepancy in image grading was due more to the difference in the acquisition of the image than to the grading criteria used. In this retrospective study, image data obtained by multiple ultrasonographers have resulted in accentuated study variables, while quantitative PD index appears to be reliable as an experienced radiologist did this in the current study.[15] Finally, because there were variations in PDUS models involved in this retrospective study, the method of data acquisition of these models may be different. Previous studies, however, suggest that different ultrasonography machines can provide equivalent examination

results concerning the pannus vascularity by adjusting the PRF value.[41] In this study, the PD signals of two models of ultrasonography machines were obtained by setting the PRF value between these models as close as possible.

In conclusion, composite assessment of PDUS and MRI greatly improved the predictive value in radiographic progression compared to MRI or PDUS alone. Our results support the fact that synovitis on PDUS and BME on MRI should be an index of therapeutic efficacy, and may therefore be of value in making judgments about additional treatment with DMARDs or to change to early biologic agent therapy. Including both synovitis on PDUS and BME on MRI as a guide to make therapeutic decisions at early stages would have benefits for RA patients. Although we assessed MR data using contrast MRI in our study, it might not require a contrast agent because BME can also be evaluated on non-contrast MRI. Taken together, these results suggest that composite assessment of PDUS and MRI may have a stronger predictive value in radiographic progression than MRI or PDUS alone in RA.

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