ORIGINAL ARTICLE

Improvement of large-joint ultrasonographic synovitis is delayed in patients with newly diagnosed rheumatoid arthritis: results of a 12-month clinical and ultrasonographic follow-up study of a local cohort

Halil Harman[1] · İbrahim Tekeoğlu[1] · Sibel Takçı[2] ·
Ayhan Kamanlı[1] · Kemal Nas[2] · Sibel Harman[3]

Abstract We analyzed the longitudinal changes in gray-scale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) parameters and correlated them with clinical, functional, and radiologic outcomes in patients with newly diagnosed rheumatoid arthritis (RA). GSUS and PDUS examinations, 44-joint disease activity score (DAS44) calculations, measurements of erythrocyte sedimentation rate, and C-reactive protein levels were performed in 68 RA patients at baseline and after 1, 3, 6, 9, and 12 months. Metacarpophalangeal joints, wrist, elbow, knee, ankle, metatarsophalangeal joints, and wrist and ankle tendons were examined by GSUS and PDUS. The laboratory and clinical findings began to decrease significantly at 1 month ($P<0.05$). Improvement of the ultrasonography (US) variables began at 3 months. After 6 months, all of the joint synovitis scores, except those of the knee, elbow, and ankle joints, showed a statistically significant reduction compared to baseline scores ($P<0.001$). DAS44 scores were lower in the very early RA group at 12 months compared to those whose symptom duration was greater than 3 months of RA (respectively, 1.53 ± 0.34; 1.80 ± 0.38; $z=-2501$, $P=0.012$). The total modified Sharp scores at 12 months correlated with total PDUS synovitis scores at 12 months ($r=0.354$, $P=0.003$). Regression of US synovitis at large joints such as the knee, elbow, and ankle tended to be delayed compared to that at small joints. PD synovitis that is persistent despite disease-modifying anti-rheumatic drug therapy may cause radiographic bone erosions.

Keywords Inflammation · Large joint · Remission · Rheumatoid arthritis · Synovitis · Ultrasonography

Introduction

Assessment of disease activity in rheumatoid arthritis (RA) is important for monitoring treatment efficiency and predicting the disease outcome. Thus, a thorough clinical examination and sensitive imaging methods are required to monitor the disease process. Clinical remission is a realistic therapeutic goal in patients with RA [1].

In particular, gray-scale ultrasonography (GSUS) to detect synovitis and power Doppler (PD) signals at multiple joint levels are valid disease activity markers in RA that are modified after effective therapy [2]. PD serves as a useful adjunct to gray-scale imaging, in that it is more sensitive for the detection of early disease, and can more accurately differentiate between chronic and acute disease in the thickened synovium [3]. There are few studies on the predictive value of longitudinal ultrasonography (US) joint assessment in the areas of disease activity, functional status, and ultrasonographic progression in early RA [4, 5]. We analyzed the longitudinal changes in GSUS and PD ultrasonography (PDUS) parameters to correlate them with the clinical, functional, and radiologic outcomes in patients with newly diagnosed RA, who had started treatment with disease-modifying anti-rheumatic drugs (DMARDs) and low-dose corticosteroids.

✉ Halil Harman
drhharman@yahoo.com

[1] Department of Physical Medicine and Rehabilitation, Rheumatology, Faculty of Medicine, Sakarya University, Sakarya, Turkey

[2] Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Sakarya University, Sakarya, Turkey

[3] Department of Radiology, Sakarya Training and Research Hospital, Sakarya, Turkey

Methods

This prospective study included 72 newly diagnosed RA patients according to the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) RA 2010 classification criteria between January 2012 and September 2013. Patients were recruited from the outpatient rheumatology clinics at the same center and consecutively included the ACR/EULAR 2010 RA classification criteria feature evaluation of (a) joint involvement, (b) rheumatoid factor (RF) and anti-citrullinated protein antibody (anti-cyclic citrullinated peptide (CCP)) levels, (c) acute phase reactant levels, and (d) duration of symptoms [6]. The study protocol was approved by our local ethics committee, and informed consent was obtained from all patients. Patients with cancer, those with any hematological abnormality, those who were pregnant or in the recent post-partum period (6 months), and those who had previously taken low-dose corticosteroids or synthetic DMARDs were excluded.

Gender, age, DMARD type, body mass index (BMI), the time elapsed from when the first clinical symptoms developed, the number of tender and swollen joints, and the patient's assessment of disease activity (0–10 scale) were noted. Initially, patients received synthetic DMARDs or corticosteroids (<10 mg/day). If the clinical response (improvement of the 44-joint disease activity score [DAS44] <0.6) was inadequate at 3 months, another synthetic or biologic DMARD was added to the therapy. Disease activity was assessed by calculating the DAS44 value for each patient at each visit [7].

DAS44 assessment includes the following joints: sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP), knee, ankle, and metatarsophalangeal (MTP). A DAS44 value <1.6 indicates remission, between 1.6 and 2.4 indicates low disease activity, between 2.4 and 3.7 indicates moderate disease activity, and >3.7 indicates high disease activity [7]. To evaluate quality of life, we used the Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) (consisting of 30 questions) [8].

Laboratory assessment included measurement of erythrocyte sedimentation rate (ESR) and assay of the levels of C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibody. The ESR was measured immediately after blood collection using a Greiner SRS 20/II instrument (Vacuette Greiner, Austria). RF and CRP levels were measured by nephelometric methods, using an IMAGE 800 analyzer (Beckman Coulter Inc., USA). Anti-CCP antibodies were measured via enzyme-linked immunosorbent assay (ELISA), and a result was considered positive if the level was above a cutoff of five arbitrary units (as suggested by Abbott ARCHITECT i1000SR).

US

Hand, wrist, elbow, knee, ankle, and toe joints were evaluated via GSUS and PDUS. Fourteen joint regions (thus, 28 in both extremities) were evaluated. These included the first through to the fifth MCP joints, the radiocarpal, ulnocarpal, and intercarpal compartments of the wrist; the humeroradial and humeroulnar compartments of the elbow; the suprapatellar and medial and lateral parapatellar recesses of the knee; the tibiotalar, talonavicular, and posterior subtalar compartments of the ankle; and the first through to the fifth MTP joints. The MCP and MTP joints were scanned at palmar/plantar and dorsal sites; wrist joints were scanned at dorsal sites. All of the patients were examined by a trained ultrasonographer with 3 years of experience (US1), after which examinations were repeated by another trained ultrasonographer with 1 year of experience (US2); both clinicians had a rheumatology background. US examinations were repeated at each visit (baseline, 1, 3, 6, 9, and 12 months). The settings for the GSUS and PDUS were the same for all patients. US examinations were completed in 30 min, and all of the images were stored. A US platform featuring a 5–13-MHz linear array transducer was employed to this end (LOGIQ P5; General Electric, New York, NY).

Synovitis was classified on gray-scale images using a semiquantitative scoring method. We considered only synovial proliferation as a sign of synovitis (not synovial effusion). The approach features use of a 0–3 scale, in which 0 corresponds to no synovitis, 1 to mild synovitis, 2 to moderate synovitis, and 3 to severe synovitis [9]. Grade 1 synovitis may occur in normal populations, and for this reason, patients of grades 2 and 3 (only) were considered to have abnormal synovitis [9]. Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing grade 2 and 3 synovitis. The range of total GSUS synovitis score was 0–84. Also, GSUS synovitis score was calculated for each joint. Mean value of each joint was calculated by using the formula.

Mean value of each joint

$$= \text{Each joint GSUS synovitis score } / \ 136$$

The maximal area of augmentation on PDUS was recorded using a previously described semiquantitative technique featuring use of a 0–3 scale, in which 0 corresponds to normal/ minimal vascularity, 1 to mild hyperemia (single vessel signal), 2 to moderate hyperemia (confluent vessels), and 3 to marked hyperemia (vessel signals in >50 % of the joint area) [10]. Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing each semiquantitative grade. The range of total PDUS

synovitis score was 0–84. Also, PDUS synovitis score was calculated for each joint. Mean value of each joint was calculated by using the formula.

Mean value of each joint

$$= \text{Each joint GSUS synovitis score} / 136$$

The PD signal was used to differentiate patients with active synovitis and tenosynovitis from those with persistent synovitis and tenosynovitis (Figs. 1 and 2).

Tenosynovitis was recorded in the extensor digitorum carpi, the extensor carpi ulnaris, in each of the five flexor digitorum tendons of the hand, the tibialis posterior, and the peroneus tendons of the ankle (thus a total of 18 tendons in both extremities). A four-grade semiquantitative scoring system (i.e., grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) was used to score tenosynovitis revealed on GSUS [11]. Semiquantitative scoring method was evaluated for each of 18 tendon regions, and total tenosynovitis scores were calculated by summing each semiquantitative grade. The range of total GSUS tenosynovitis score was 0–54. Also, GSUS tenosynovitis score was calculated for each tendon. Mean value of each tendon was calculated by using the formula.

Mean value of each tendon

$$= \text{Each tendon GSUS tenosynovitis score} / 136$$

A four-grade semiquantitative scoring system (i.e., grade 0, no Doppler signal; grade 1, minimal signal; grade 2, moderate signal; grade 3, severe signal) was used to score pathological peritendinous PD signals within the synovial sheath [11]. Semiquantitative scoring method was evaluated for each of 18 tendon regions, and total PD tenosynovitis scores were

calculated by summing each semiquantitative grade. The range of total PDUS tenosynovitis score was 0–54. Also, PDUS tenosynovitis score was calculated for each tendon. Mean value of each tendon was calculated by using the formula.

Mean value of each tendon

$$= \text{Each tendon PDUS tenosynovitis score} / 136$$

Radiographic assessment

Posteroanterior radiographs of the patients' wrists and anteroposterior radiographs of the patients' feet were obtained at baseline and at the 12-month follow-up. The radiographs were read by an independent radiologist, who was blinded regarding the clinical, laboratory, and PDUS findings. Radiologic damage was assessed according to the van der Heijdemodified Sharp method [12]. This method measures erosions (score range 0–280) and joint space narrowing (score range 0–168) in 44 different joints and provides a sum score ranging from 0 to 448.

Statistical analysis The SPSS software (IBM SPSS statistics version 20.0) was used for statistical analysis. Quantitative variables (clinical, laboratory, and US parameters) are given as means with SDs and ranges. Upon univariate analysis, the Mann-Whitney U test was used to compare continuous variables and the chi-square test to compare categorical variables. Spearman's correlation coefficients between radiographic and sonographic findings were calculated. To compare clinical and ultrasonographic parameters with radiographic progression, changes in each parameter during the study were evaluated by calculating time-integrated values throughout the year

Fig. 1 Longitudinal image of the radiocarpal and midcarpal joint showing grade 3 synovitis with grade 2 power Doppler signal
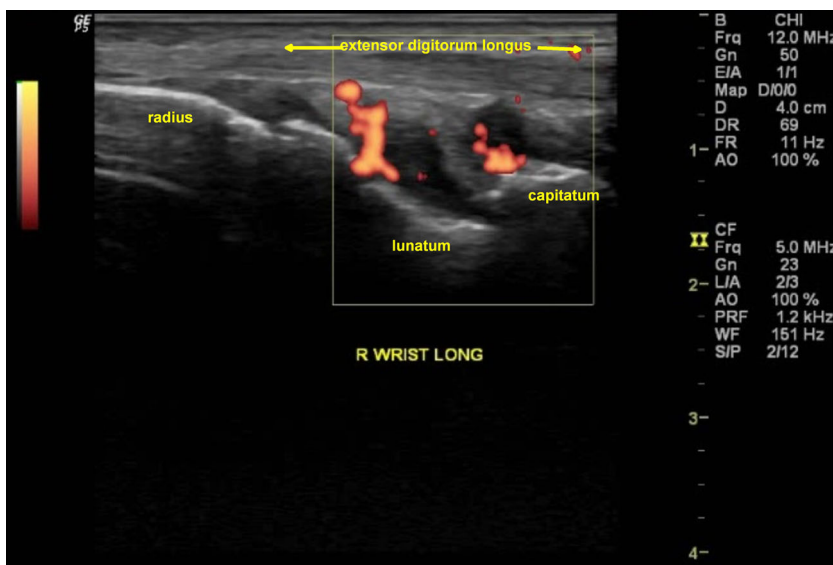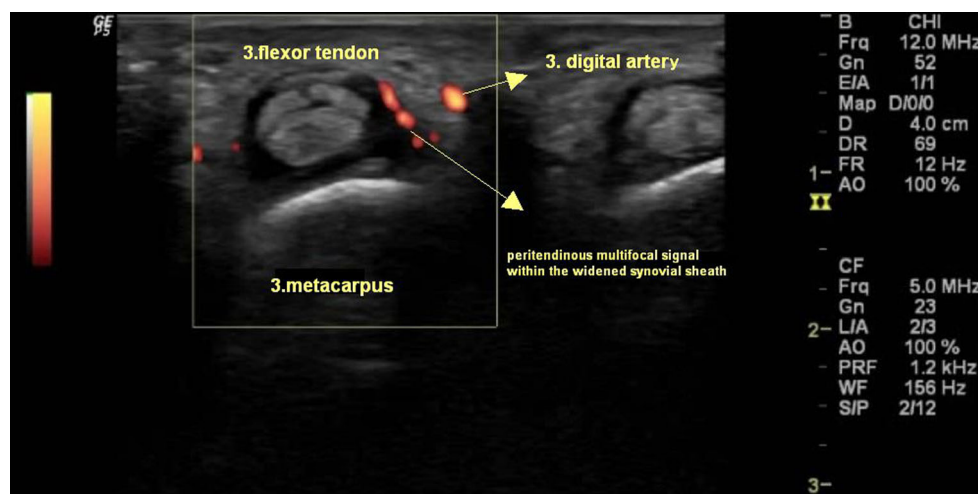
Fig. 2 Transverse image of the flexor tendons of the third finger showing grade 2 tenosynovitis with grade 2 power Doppler signal

using the area under the curve (AUC) method [27]. A *P* value less than 0.05 was considered to indicate statistical significance. The course of the clinical, laboratory, and US variables was obtained by calculating time-integrated values using the AUC method. Unweighted kappa statistics were used to calculate interobserver agreements for diagnosis of synovitis, tenosynovitis, PD synovitis, and PD tenosynovitis. Interobserver agreement was performed for all patients in baseline visit and at the end of follow-up.

Results

Baseline clinical and laboratory findings

We included 72 newly diagnosed RA patients aged 18–78 years. Available data from four patients with incomplete follow-up were excluded from the study. The principal demographic and clinical features are summarized in Table 1. In total, 78 % were RF-positive and 85 % were anti-CCP-positive. The average ESR and CRP values for all of the patients were 42.47 mm/h and 30.98 mg/dL at baseline, respectively (ESR 0–20 mm/h, CRP 0–5 mg/dL, normal range).

Of a total of 1904 examined joint regions, 13.2 % ($n=253$) of all examined joints had tender joints and 10.5 % ($n=201$) had swollen joints. On clinical examination, tenderness was predominantly observed in the wrist, MCP2, and ankle joints (25.2, 17.5, and 10.5 %, respectively); swelling was predominantly observed in the wrist, MCP2, and ankle joints (21.5, 16.5, and 9.5 %, respectively).

At inclusion, all patients were administered methotrexate (10–15 mg/week) and low-dose prednisone or methylprednisolone. After the 12-month follow-up, 43 (63.3 %) patients were taking one DMARD and 21 (30.9 %) were taking two or more synthetic DMARDs. Three patients (4.4 %) had started therapy with adalimumab, and one (1.4 %) had started therapy with golimumab. All of the patients who started tumor necrosis factor (TNF) blocker therapy were established RA. One patient had pulmonary involvement of RA at 1-year follow-up.

Table 1 Clinical characteristics of 68 study patients with rheumatoid arthritis

Age, mean [IQR]±SD (years)	55.88±15.92 [56.5]
Sex (% women)	70.8
BMI, mean [IQR]±SD (kg/cm^2)	27.60±3.02 [27.50]
Time elapsed from first clinical symptoms, mean [IQR]±SD (years)	0.63±0.61 [0.62]
DAS44 scores at baseline, mean [IQR]±SD	3.34±0.53 [3.32]
Swollen joint counts at baseline, mean [IQR]±SD	3.57±2.30 [6.00]
Tender joint counts at baseline, mean [IQR]±SD	6.07±2.99 [6.00]
RAQoL total scores at baseline, mean [IQR]±SD	21.49±5.63 [3.50]
Receiving synthetic DMARD monotherapy after 12 months (% patients)	63.3
Receiving two or more synthetic DMARD therapy after 12 months (% patients)	30.9
Receiving biologic DMARDs during after 12 months (% patients)	5.8

BMI body mass index, *RAQoL* Rheumatoid Arthritis Quality of Life, *DMARD* disease-modifying anti-rheumatic drugs, *IQR* interquartile range, *SD* standard deviation

According to the DAS44 score, 3.0 % (n=2) of patients exhibited low-level disease activity, 76.4 % (n=52) exhibited moderate disease activity, and 20.6 % (n=14) exhibited high-level disease activity at baseline. According to the DAS44 score, 48.5 % (n=33) of patients were in remission (DAS44 <1.6), 48.5 % (n=33) exhibited low-level disease activity, and 3.0 % (n=2) exhibited moderate disease activity at the 12-month follow-up.

Baseline ultrasonography findings

A total of 1904 joints were examined by US in all of the RA patients. Of these joints, GSUS synovitis was detected in 17.0 % (n=324) of joints and PDUS synovitis was detected in 13.7 % (n=261) of joints. GSUS synovitis was predominantly observed in the wrist, MCP2, and ankle joints (31.12, 21.8, and 12.5 %, respectively); PDUS synovitis was predominantly observed in the wrist, MCP2, and ankle joints (26.7, 18.5, and 10.7 %, respectively). A total of 1224 tendons from all of the RA patients were examined by US. Of these tendons, GSUS tenosynovitis was detected in 8.4 % (n=138) of tendons and PDUS tenosynovitis was detected in 6.8 % (n=111) of tendons. GSUS tenosynovitis was observed in the extensor carpi ulnaris, second flexor digitorum, and tibialis posterior tendon (29.4, 18.3, and 9.5 %, respectively); PDUS tenosynovitis was predominantly observed in the extensor carpi ulnaris, second flexor digitorum, and tibialis posterior tendon (25.7, 15.4, and 9.5 %, respectively).

Baseline radiographic findings

Baseline and 12-month radiographs were available for 54 patients. The total mean (±standard deviation [SD]) modified Sharp score was 15.03±4.31 at the study entry. The erosion score mean±SD was from 8.54±2.34 at the study entry. The joint space narrowing (JSN) score mean±SD was 7. 03± 3.45 at the study entry.

Laboratory, ultrasonographic, and radiographic course

The mean ESR and CRP values decreased significantly from baseline to 1 month and from 1 to 3 months. Laboratory values tended to be stable at other visits. The VAS and DAS44 values decreased significantly throughout the follow-up period.

Improvement of US variables began at 3 months. The course of clinical, laboratory, and US variables throughout the study is shown in Table 2. Wrist GSUS synovitis and PDUS synovitis, as well as wrist GSUS tenosynovitis and PDUS tenosynovitis scores, showed a statistically significant decrease from baseline to 3 months. At the 6-month follow-up, all of the joint synovitis scores, except those of the knee, elbow, and ankle joints, showed a statistically significant

reduction compared to those at baseline. Finally, the ankle, knee, and elbow synovitis scores were decreased at the 9-month follow-up (Fig. 3a–e).

The total mean±SD modified Sharp scores increased from 15.03±4.31 at the study entry to 23.31±5.39 at 12 months. The erosion score mean±SD increased from 8.54±2.34 at the study entry to 16.54±4.32 at 12 months. The JSN score mean±SD increased from 7.03±3.45 at the study entry to 9.35± 3.19 at 12 months.

Correlation between radiography or ultrasonography and clinical variables

Patients whose symptom duration was less than 3 months were classified as having very early RA. DAS44 scores were lower in the very early RA group at 12 months than in those whose symptom duration was longer than 3 months (1.53± 0.34 and 1.80±0.38, respectively; z=−2.501, P=0.012).

The correlations between the time-integrated values of the clinical and US parameters and the outcome variables are displayed in Table 3. The time-integrated values of total GSUS synovitis scores and total PDUS synovitis score demonstrated stronger significant correlations with the progressions in radiographic erosion score, JSN scores, and total radiographic scores. There was not a significant correlation between the time-integrated values of total tenosynovitis and total PD tenosynovitis scores and the progressions in radiographic scores. The time-integrated values of the US parameters demonstrated a significant correlation with the DAS44 after 1 year.

Interobserver reliability of ultrasonography

The extent of interobserver agreement was 87, 91, 77, and 92 % for the presence/absence of GSUS synovitis, PDUS synovitis, GSUS tenosynovitis, and PDUS tenosynovitis with κ values of 0.70, 0.72, 0.64, and 0.78, respectively.

Discussion

We found a significant improvement in the clinical and laboratory indices earlier than GSUS and PDUS parameters throughout the present study. We showed that the improvement of large-joint US synovitis such as that of the knee, elbow, and ankle tended to be delayed compared to small-joint US synovitis. This issue was the main focus of our study. Radiographic worsening was observed in patients with late diagnosis with a persistent PD signal. Therefore, the treatment regimen should be planned for the prevention of persistent PD synovitis.

The primary objective of our study was to analyze the longitudinal changes for rigorous US examination. Although

Table 2 Clinical, laboratory, and ultrasonographic course in patients with rheumatoid arthritis (n=68)

Parameter	Baseline	1 month	3 months	6 months	9 months	12 months
Pain, 0–10-mm VAS	7.31±1.54	5.32±1.25***	4.00±1.16***	3.60±0.95*	2.76±1.10***	2.39±0.74*
ESR (mm/h)	42.47±24.69	23.5±15.64***	16.00±12.26***	13.73±7.66	13.20±7.35	11.34±6.79
CRP (mg/dL)	30.98±31.20	13.19±11.43***	8.54±8.37**	9.20±12.22	7.20±9.21	6.44±2.42
DAS44 score	3.34±0.53	3.02±0.49***	2.57±0.48***	2.05±0.46***	1.85±0.42**	1.69±0.40*
RAQoL score	21.49±5.63	20.21±5.25	15.72±3.94**	14.49±12.70	13.52±9.54	9.64±3.67**
Total GSUS synovitis score	11.25±4.75	11.22±4.64	7.81±5.11***	4.77±3.74**	3.17±2.17	1.47±0.92**
Total PDUS synovitis score	9.05±4.38	8.50±4.12	3.57±2.74***	1.17±1.08***	075±0.71	0.52±0.44
Total GSUS tenosynovitis core	4.80±2.23	4.67±2.23	1.85±1.63***	1.15±1.39	0.65±0.95	0.37±0.52
Total PDUS tenosynovitis score	3.85±3.06	2.97±2.08	1.18±1.30***	0.25±0.41	0.22±0.20	0.00±0.00*

VAS visual analog scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS44* 44-joint disease activity score, *RAQoL* Rheumatoid Arthritis Quality of Life Questionnaire, *PDUS* power Doppler ultrasound, *GSUS* gray-scale ultrasonography

*$p<0.05$ versus the preceding visit, by pairwise comparison; **$p<0.01$ versus the preceding visit, by pairwise comparison; ***$p<0.001$ versus the preceding visit, by pairwise comparison

we found many longitudinal studies in the literature that evaluated the joint inflammatory activity of the wrist and finger joints in patients with RA by GSUS and PDUS, studies on large joints such as the knee, elbow, and ankle are scarce. Most of the follow-up studies were mainly performed on the wrist and finger joints of RA patients treated with TNF blockers. DAS28 scores were used to evaluate disease activity in those studies. In one of those studies, improvement of PD signals
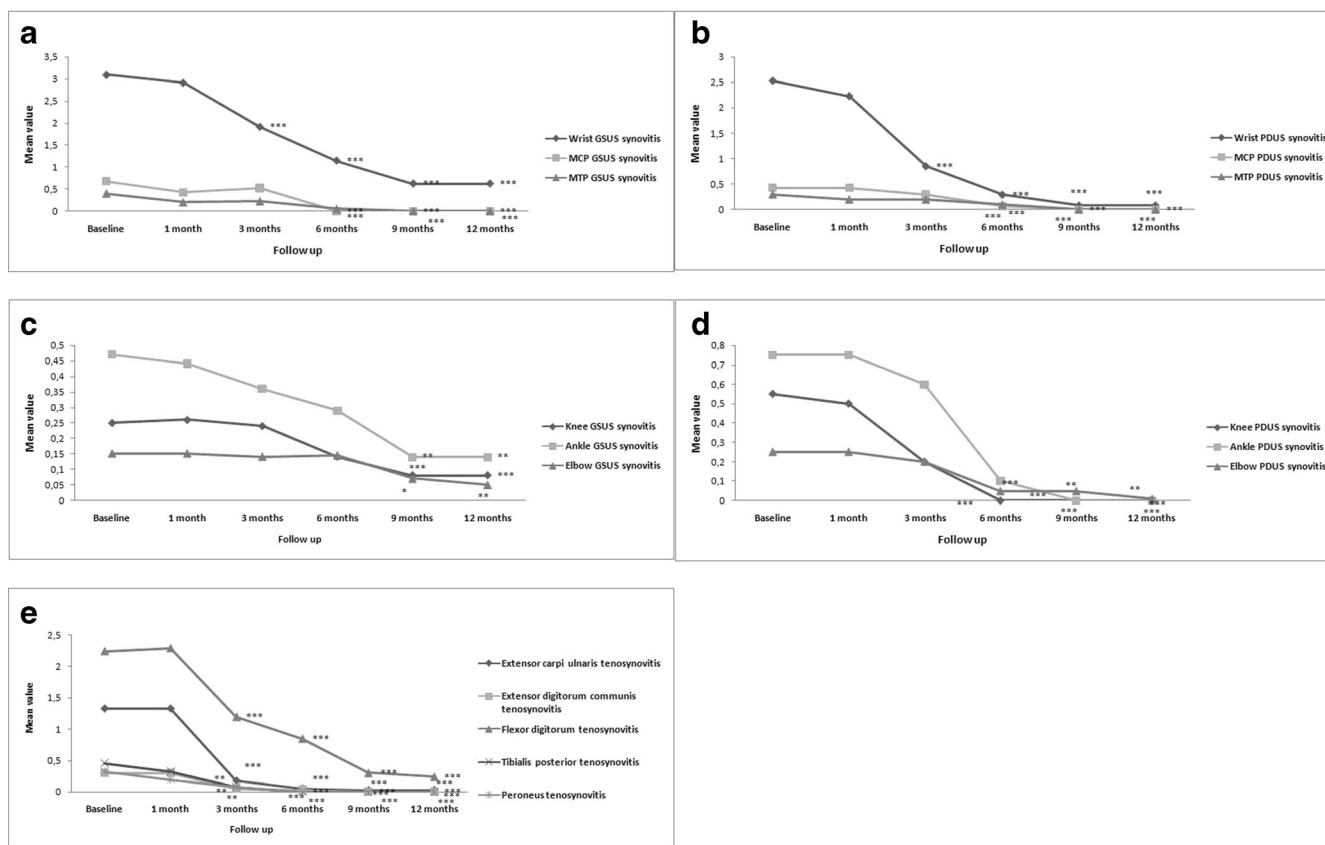

Fig. 3 Changes in the mean values of all joints at GSUS and PDUS throughout the follow-up period in 68 rheumatoid arthritis patients. **a** Wrist, MCP, and MTP joints at GSUS. **b** Wrist, MCP, and MTP joints at PDUS. **c** Knee, ankle, and elbow joints at GSUS. **d** Knee, ankle, and elbow joints at PDUS. **e** Extensor carpi ulnaris, extensor digitorum carpi, flexor digitorum, tibialis posterior, and peroneus tendons at gray-scale ultrasonography. *$p<0.05$ versus the baseline, by pairwise comparison; **$p<0.01$ versus the baseline, by pairwise comparison; ***$p<0.001$ versus the baseline, by pairwise comparison. *PDUS* power Doppler ultrasonography, *GSUS* gray-scale ultrasonography, *MCP* metacarpophalangeal, *MTP* metatarsophalangeal

Table 3 Correlation between time-integrated value of clinical and ultrasonographic parameters and disease activity (DAS44) and radiologic outcome at 1 year of follow-up

TIV	DAS44 1 year	Erosion score progression	JSN score progression	Total score progression
Tender joint count	0.35*	0.45*	NS	0.33*
Swollen joint count	0.31*	0.53**	NS	0.35*
DAS44	0.79***	0.39*	NS	0.37*
Total GSUS synovitis scores	0.38**	0.65**	0.36*	0.54**
Total PDUS synovitis scores	0.39**	0.67***	0.38*	0.56***
Total tenosynovitis scores	0.36**	NS	NS	NS
Total PD tenosynovitis scores	0.41**	NS	NS	NS

DAS44 disease activity score 44, *GSUS* gray-scale ultrasonography, *JSN* joint space narrowing, *NS* nonsignificant, *PDUS* power Doppler ultrasound, *TIV* time-integrated value

*$p < 0.05$; **$p < 0.01$; **$p < 0.001$

was observed from 2 to 6 weeks after TNF blocker treatment had begun at the finger joints [13].

Iagnocco et al. [14] also found significant improvement of US synovitis in the finger, wrist, and knee joints 3 months after the start of TNF blocker treatment. This study did not evaluate the 1-month follow-up. Naredo et al. [15] suggested that improvement of GSUS and PDUS synovitis started 1 month after TNF blocker treatment. However, this study did not include ultrasonographic assessment of each joint follow-up, and the patients included in the study had long-standing RA. Hartung et al. [16] only evaluated the ultrasonographic assessment of large joints such as the elbow, hip, knee, and shoulder at the 1-year follow-up and concluded that improvement of GSUS and PDUS synovitis scores at large joints began in the third month. The patients received synthetic DMARDs and/or biologic DMARDs in the present study and had established RA; the results were not compared to joints such as MTP and ankle joints. Backhaus et al. [17] studied the effect of various therapies on ultrasonographic erosions. The patients, switched from one biologic to another, exhibited a significant decline in erosions after 12 months, while the erosion scores in the other groups were stable. The present study included the wrist, MCP 2 and 3, PIP 2 and 3, and MTP 2 and 5 joints. A limitation of this study was that large joints were not considered for ultrasonographic examination.

In the current study, patients were newly diagnosed with RA, and involvement of large joints showed a delayed ultrasonographic response to treatment as observed at the early stage of the disease. Synthetic DMARD and low-dose corticosteroid therapy were administered to the patients as first-line treatment, followed by TNF blocker treatment according to the patients' clinical and laboratory response. We applied TNF blocker treatment in only four patients. It took 3 months to receive an ultrasonographic response from the patients with synthetic DMARD and low-dose corticosteroid therapy. On the other hand, regression of large-joint US synovitis appeared at the ninth month. Considering the design of our study, we

believe that our data are more amenable regarding daily practice and will provide guidance to rheumatologists who perform ultrasonographic follow-up of patients. We suggest that US synovitis of large joints is delayed because suppression of inflammation is more difficult in these joints and more aggressive immunosuppression is needed. Kanazawa et al. [18] proposed that the prevalence of large-joint involvement might be higher since they are subjected to higher mechanical loading than smaller joints and are, therefore, more susceptible to inflammation. In the current study, a decline in inflammatory markers was observed starting during the first month. During the follow-up, laboratory markers were stable after the third month. Consistent with our results, other studies found an improvement of laboratory findings 1 month after therapy [15, 16].

In the present study, we demonstrated that high baseline PD scores were not closely associated with radiographic worsening; however, persistence of the PD signal led to radiographic deterioration. The current results are in agreement with those of previous studies [19, 20]. In addition, lower radiographic damage scores in very early RA cases are indicators of the importance of early diagnosis and treatment. Ultrasonographic follow-up of tenosynovitis distinguishes the present work from those of previous studies. The results of this study showed that tenosynovitis of the wrist and ankle joints responds to standard DMARD and low-dose corticosteroid therapy within 3 months. One of the advantages of our study is its convenience for daily practice, application of DMARD therapy right after initial RA diagnosis, and the clinical and ultrasonographic follow-up. The follow-up of frequently involved large joints, as well as those of small joints, is an additional advantage. Moreover, the third advantage is that our study cohort was composed of newly diagnosed, previously untreated RA patients. Our study had some limitations. Particularly, we cannot explain all of our observations, possibly because although interobserver reliability was good to excellent, patients were evaluated by different clinicians at different times and intrareader reliabilities for PDUS synovitis and GSUS

synovitis scoring could not be calculated. The prevalence of PDUS findings was relatively low compared to that in other studies. This may be caused by the relatively high pulse repetition frequency (1.2 kHz). Also, the machine, which is middle-size ultrasound equipment, may not be performing well for PDUS examination.

In conclusion, our data encourage clinicians to use US to determine synovitis in newly diagnosed RA patients at the follow-up, as well as during clinical and laboratory evaluations. Considering the US findings, persistent synovitis with a PD signal despite DMARD therapy may cause radiographic bone erosions. US findings are supplementary to standard clinical evaluation in multiple joint assessment. However, clinicians must be careful concerning the persistence of large-joint US synovitis.

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