The synovial grade corresponding to clinically involved joints and a feasible ultrasound-adjusted simple disease activity index for monitoring rheumatoid arthritis

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Abstract

Objectives: To determine which grade of ultrasound (US) synovitis corresponds to clinically involved joints in rheumatoid arthritis (RA) and develops a new US-adjusted composite measure.

Methods: Clinical and US examinations were performed on 137 patients with RA (28 joints). Synovial effusion, hypertrophy, and blood flow were semiquantitatively graded from 0 to 3 using gray scale (GS) and power Doppler (PD) modes. We calculated US-adjusted simple disease activity index (SDAI) and assessed feasibility, and external validity by comparing with erythrocyte sedimentation rate (ESR), and modified health assessment questionnaires (MHAQ).

Results: GS ≥2 and PD ≥0 corresponds to clinically swollen joints, and GS ≥2 and PD ≥1 corresponds to tender joints. The US-adjusted SDAI showed the highest correlation when US-determined swollen joints were defined as PD ≥2 with ESR, and GS ≥3 and PD ≥2 with MHAQ. A feasible US-adjusted SDAI examining only clinically involved joints still showed a higher correlation with ESR and MHAQ than SDAI.

Conclusion: Our composite measure complemented by US only for clinically involved joints is feasible and reliable for monitoring disease activity.

Introduction

To protect bone from irreversible destruction, diagnosis should be made and treatment should be commenced in patients with rheumatoid arthritis (RA) in the early stages of the disease [1–4]. Treatment must be maintained without interruption, and intensive monitoring of disease activity and the adjustment of treatment have been recommended [5–7]. The accepted composite measures of disease activity, including joint assessment, are recommended and widely used in routine clinical practice to guide treatment decisions [8–11]. However, high intra- and interobserver variability in clinical joint assessment is unavoidable [12–15]; therefore, there is concern that the disease activity status of some patients with RA may be defined incorrectly because of inaccurate assessments of the involved joints.

High-resolution ultrasound (US) examination can be used to visualize anatomically involved joints with synovial hypertrophy/effusion using the gray scale (GS) mode, whereas the power Doppler (PD) mode can be used to assess the degree of synovial inflammation. This method shows superior sensitivity and interobserver reliability in the detection of synovitis in patients with RA compared to clinical examinations [16–22]. Recently, joint counts determined by US or a combination of clinical and US examinations have been reported to be more reliable in assessing disease activity than clinical examination alone [23,24]. These proposed joint numbers for US examination range from 22 to 28; however, they may not be suitable in outpatient settings due to non-negligible joint numbers requiring effort and expense. US allows clinicians to make quick diagnosis and treatment decisions; thus, it would be desirable if the efficacy of US for fewer joints can be verified and US can be utilized by attending physicians during physical examination at the site as point of care testing.

The primary objective of this study was to determine which grade of US synovitis corresponds to clinically involved joints. Second, we aimed to develop a feasible and reliable US-adjusted composite measure that can be used during routine clinical examinations.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki and approved by our Institutional Review Board. Informed consent was obtained from all included patients. RA was diagnosed based on the criteria established in 1987 [25]. By using data derived from our previous study [26], we performed a secondary analysis here.

All patients in the current study were examined clinically for joint swelling and/or tenderness. Examinations were performed by rheumatologists blinded to the US findings. Clinical examinations were followed by an independent US examination within 30 min.
Experienced rheumatologists performed US examination using ProSound Alpha 7 with UST-5411, 10–13 MHz transducer (Hitachi Aloka Medical, Ltd., Tokyo, Japan).

Clinical and US examinations were performed on 28 joints: the first interphalangeal (IP) joint, proximal interphalangeal (PIP) joint, metacarpophalangeal (MCP) joint, wrist, elbow, shoulder, and knee on both sides. Synovial effusion and/or hypertrophy was defined as the presence of abnormal hypoechoic material within the joint recesses, tendon sheaths, or bursa, and it was graded on a semiquantitative scale ranging from 0 to 3 [27,28]. Synovial blood flow was evaluated by PD signals for each of the intra-articular and periarticular synovial sites. The PD signal parameters were adjusted to the lowest permissible pulse repetition frequency to maximize sensitivity. PD signals in the intra-articular, periarticular synovial sites, tendon sheaths, and bursa were graded on a semiquantitative scale, ranging from 0 to 3 [27,28]. The maximum GS/PD grade recorded for multiple synovial sites for a given joint region was recorded as the GS/PD grade for the respective joint.

The intra-rater reliability of US examinations was evaluated by using randomly selected stored US images (a total of 48 images for each US examiner). US examiners graded them again and were blinded to the results of the previous assessment. The inter-rater reliability between US examiners was evaluated with the same sets of images graded by other examiners at the end of the study period.

In this secondary study, we performed subsequent analyses, as follows.

**Gray scale/power Doppler grading for swollen/tender joints**

We investigated the possible combinations of GS and PD to identify the grade with the highest concordance rate (κ coefficient) with clinically determined joint swelling and tenderness. We also determined the difference in the GS grade and concordance rate (κ coefficient) between various joints separately.

**Ultrasound-determined swollen joints and the ultrasound-adjusted simple disease activity index**

Joints with US findings for all GS/PD possible grade combinations were assumed as US-determined swollen joints. The US-adjusted simple disease activity index (US-adjusted SDAI) was calculated by substituting the US-determined swollen joint count for the SJC in the SDAI [11] calculation.

**External validity**

To determine which GS/PD grade combination of the US-adjusted SDAI has the highest validity for inflammation and function disability, we analyzed Pearson’s correlation coefficient between the US-adjusted SDAI/SDAI and erythrocyte sedimentation rate (ESR) or modified health assessment questionnaire (MHAQ) [29], p values less than 0.05 were considered significant unless otherwise specified.

**Feasibility assessment**

It was easier to use US in routine clinical assessments when fewer joints were assessed. To determine a potential feasible method for utilizing the US-adjusted SDAI in the clinical setting, we examined the reliability of the US-adjusted SDAI, where US-determined joints were selected only from clinically swollen and/or tender joints.

**Results**

The study population consisted of 137 consecutive patients with RA (108 women, 29 men) aged 22–85 years at Juntendo University Hospital in Tokyo, Japan (Supplementary Table 1).

The intra- and inter-rater reliability of the GS and PD grade were evaluated using intraclass correlation coefficients (ICCs). ICCs for the intrarater reliability of the GS and PD grade were 0.92 (95% confidence interval (CI): 0.87–0.95, p < 0.001) and 0.97 (95% CI: 0.95–0.98, p < 0.001), respectively. ICCs for the inter-rater reliability of the GS and PD grade were 0.91 (95% CI: 0.82–0.95, p < 0.001) and 0.96 (95% CI: 0.93–0.98 p < 0.001), respectively. These data suggest that the US data were reproducible and reliable.

Clinically determined joint swelling had the highest concordance rate with US-determined joint score of GS ≥2 and PD ≥0. Clinically determined joint tenderness was most reliable at US-determined joint grade of GS ≥2 and PD ≥1 (Table 1). However, agreement between the clinically determined joint tenderness and US findings was poor; in most cases, joint tenderness might not correlate with US synovial hypertrophy/effusion or PD signals. These results indicate that joint tenderness determined by clinical examination should not be substituted or modified according to US findings. Therefore, we decided to calculate US-adjusted SDAI only by replacing the SJC in SDAI with US-determined swollen joint count.

GS grade corresponded to clinically determined joint swelling and the κ coefficients for each joint were different between various joints (Figure 1). Among large joints such as the shoulder and elbow, those with GS = 3 showed the highest κ coefficient, indicating low sensitivity and inaccurate assessment of the clinical examination, particularly for large joint swelling. Most of the smaller joints and the knee joint showed the highest κ coefficient with GS ≥2.

The US-adjusted SDAI was compared with SDAI (Figure 2a). Most US-adjusted SDAI besides GS ≥1 showed lower scores than SDAI. The proportion of the patients in each disease activity status was different depending on the grade of US-determined swollen joints (Figure 2b).

External validity was evaluated by comparing the correlation coefficients between the US-adjusted SDAI/SDAI and ESR and MHAQ. Although the US-adjusted SDAI and SDAI showed a statistically significant correlation with these variables, the correlation coefficient was higher for the US-adjusted SDAI than for SDAI (Table 2). The highest correlation was shown when US-determined swollen joints were defined as PD ≥2 according

### Table 1. The concordance rate (κ coefficient) between swollen/tender joints and the ultrasound-determined involved joint.

| Swollen joint | GS ≥1 | GS ≥2 | GS = 3 |
|---------------|-------|-------|--------|
| PD ≥0         | 0.357 | 0.426 | 0.411  |
| (0.28–0.44)   | (0.34–0.51) | (0.24–0.41) | |
| PD ≥1         | 0.407 | 0.398 | 0.312  |
| (0.32–0.49)   | (0.31–0.48) | (0.22–0.40) | |
| PD ≥2         | 0.360 | 0.360 | 0.276  |
| (0.27–0.45)   | (0.27–0.45) | (0.18–0.37) | |
| PD = 3        | 0.150 | 0.151 | 0.109  |
| (0.05–0.25)   | (0.05–0.25) | (0.01–0.21) | |
| Tender joint  |       |       |        |
| PD ≥0         | 0.185 | 0.267 | 0.237  |
| (0.09–0.28)   | (0.17–0.36) | (0.14–0.33) | |
| PD ≥1         | 0.273 | 0.280 | 0.232  |
| (0.18–0.37)   | (0.19–0.37) | (0.14–0.33) | |
| PD ≥2         | 0.266 | 0.262 | 0.220  |
| (0.17–0.36)   | (0.17–0.36) | (0.12–0.32) | |
| PD = 3        | 0.136 | 0.137 | 0.094  |
| (0.03–0.24)   | (0.03–0.24) | (−0.01–0.20) | |

The numbers in bold type indicate the highest κ coefficient in each table.
to ESR ($r = 0.562, p < 0.0001$), and GS $\geq 3$ and PD $\geq 2$ according to MHAQ ($r = 0.497, p < 0.0001$).

To utilize the US-adjusted SDAI in usual clinical settings, feasibility is essential. Twenty-eight joints were equally examined in all studied patients during US examination; however, the

| Table 2. Correlation coefficient between ultrasound-adjusted SDAI/SDAI and ESR/MHAQ. |
|-----------------|-----------------|-----------------|-----------------|
|                 | **ESR** | **p value** | **MHAQ** | **p value** |
| SDAI            | 0.529   | <0.0001     | 0.471   | 0.0002     |
| Ultrasound-adjusted SDAI swollen joint defined as GS $\geq 1$ | 0.550   | <0.0001     | 0.437   | 0.0005     |
| GS $\geq 2$     | 0.546   | <0.0001     | 0.424   | 0.0008     |
| GS $= 3$        | 0.526   | <0.0001     | 0.471   | 0.0002     |
| PD $\geq 1$     | 0.556   | <0.0001     | 0.472   | <0.0001    |
| PD $\geq 2$     | 0.562   | <0.0001     | 0.490   | <0.0001    |
| PD $= 3$        | 0.526   | <0.0001     | 0.486   | <0.0001    |
| GS $\geq 1$ and PD $= 0$ | 0.510   | <0.0001     | 0.439   | <0.0001    |
| GS $\geq 2$ and PD $= 0$ | 0.520   | <0.0001     | 0.439   | <0.0001    |
| GS $= 3$ and PD $= 0$ | 0.512   | <0.0001     | 0.492   | <0.0001    |
| GS $\geq 1$ and PD $\geq 1$ | 0.556   | <0.0001     | 0.472   | 0.0002     |
| GS $\geq 2$ and PD $\geq 1$ | 0.548   | <0.0001     | 0.475   | 0.0001     |
| GS $= 3$ and PD $\geq 1$ | 0.533   | <0.0001     | 0.484   | <0.0001    |
| GS $\geq 1$ and PD $\geq 2$ | 0.562   | <0.0001     | 0.490   | <0.0001    |
| GS $\geq 2$ and PD $\geq 2$ | 0.557   | <0.0001     | 0.491   | <0.0001    |
| GS $= 3$ and PD $\geq 2$ | 0.541   | <0.0001     | 0.497   | <0.0001    |
| GS $\geq 1$ and PD $= 3$ | 0.526   | <0.0001     | 0.486   | <0.0001    |
| GS $\geq 2$ and PD $= 3$ | 0.526   | <0.0001     | 0.484   | 0.0001     |
| GS $= 3$ and PD $= 3$ | 0.527   | <0.0001     | 0.491   | <0.0001    |

$r$: correlation coefficient; ESR: erythrocyte sedimentation rate; MHAQ: modified health assessment questionnaire; SDAI: simplified disease activity index; GS: gray scale; PD: power Doppler.

Figure 1. Concordance rate (κ coefficient) between clinically swollen joints and the gray scale (GS) grade for each joint region. MCP, metacarpophalangeal; PIP, proximal interphalangeal joint; IP, interphalangeal joint.

Figure 2. (a) Scores for the ultrasound (US)-adjusted simple disease activity index (SDAI) and SDAI. Joints with US findings for all possible gray scale (GS)/power Doppler (PD) grade combinations are assumed to be US-determined swollen joints. The US-adjusted SDAI is calculated by substituting the US-determined swollen joint count for the swollen joint count in the SDAI calculation. Bars represent standard deviation of the mean. (b) Disease activity status categories. Patients are categorized according to different disease activity statuses, and the proportion of the status is different depending on the grade of the assumed US-determined swollen joint (remission, ≤3.3; low, <11; moderate, 11–26; and high, >26).
A comparison between the count of clinically swollen and/or tender joints with and without power Doppler (PD) showed that the latest joints with subclinical synovitis were the clinically undetected joints with PD ≥ 2/subclinical synovitis). The joint number of clinically undetected joints with PD ≥ 2, except for the elbow and wrist joints, is the lowest in most joint regions. MCP, metacarpophalangeal; PIP, proximal interphalangeal joint; IP, interphalangeal joint.

Figure 3. (a) Clinically and ultrasound (US)-determined joint counts. The number of involved joints (clinically or by US) with all possible gray scale/power Doppler combinations in the studied patients is shown according to each disease status. Bars represent standard deviation of the mean. (b) A comparison of the joint count (%) between clinically swollen and/or tender joints with and without power Doppler (PD) ≥ 2, and clinically undetected joints with PD ≥ 2 (subclinical synovitis). The joint number of clinically undetected joints with PD ≥ 2, except for the elbow and wrist joints, is the lowest in most joint regions. MCP, metacarpophalangeal; PIP, proximal interphalangeal joint; IP, interphalangeal joint.

Discussion
Inaccurate clinical evaluations for US-determined swollen joints, particularly in larger joints such as the shoulder and elbow, suggest the need for US complementation. Composite measures complemented by US only for clinically involved joints worked effectively for assessing disease activity.

Mandl et al. [24] reported on composite measures in which the SJC was substituted by the US-determined involved joint count. Unlike our analysis, joints with values of GS ≥ 1 or PD ≥ 1 were considered involved and were counted. It remains unclear whether grade 1 for GS or PD indicates a pathological finding [30–34]. The number of joints designated as GS grade 1 in the composite measure may result in an overly sensitive and under-specific disease activity assessment. Damjanov et al. [23] reported on another composite measure, the US disease activity score (DAS), in which the SJC and tender joint count (TJC) were replaced with the US-determined involved joint count [9]. Synovial hypertrophy and/or effusion was qualitatively graded as absent (0) or present (1) and was replaced with the SJC. PD signals were graded in 22 joint set; thus, it estimates the disease activity incorrectly. It is considered that US examination can exclude non-inflammatory conditions such as bony joint swelling in osteoarthritis, the joint size difference among individuals, and fat tissue or edema, thus resulting in a more accurate assessment of disease activity.

When there is no method of determining joint swelling or tenderness clinically, imaging modalities such as radiography, US, and magnetic resonance imaging contribute to the assessment. From the viewpoint of point of care testing, US is the only method for assessing joint involvement and for providing patients with a better understanding of their disease immediately. Moreover, US is the only repeatable imaging modality that is easy and safe. With regard to consultation time, US examination for fewer joints only result in correction of SJC assessment, and it was more reliable for monitoring disease activity and functional disability. Moreover, the number of joints for US complementation is a novel point, and since these joint areas are not fixed as default conditions, they can be changed flexibly depending on each patient’s status of clinically involved joints. If the joint set to be examined by US is fixed as a default, it is possible that any joint that the patients complain about may not be included in the joint set; thus, it estimates the disease activity incorrectly. It is considered that US examination can exclude non-inflammatory conditions such as bony joint swelling in osteoarthritis, the joint size difference among individuals, and fat tissue or edema, thus resulting in a more accurate assessment of disease activity.

We demonstrated that a fewer number of joints for US examination still resulted in correction of SJC assessment, and it was more reliable for monitoring disease activity and functional disability. Moreover, the number of joints for US complementation is a novel point, and since these joint areas are not fixed as default conditions, they can be changed flexibly depending on each patient’s status of clinically involved joints. If the joint set to be examined by US is fixed as a default, it is possible that any joint that the patients complain about may not be included in the joint set; thus, it estimates the disease activity incorrectly. It is considered that US examination can exclude non-inflammatory conditions such as bony joint swelling in osteoarthritis, the joint size difference among individuals, and fat tissue or edema, thus resulting in a more accurate assessment of disease activity.

Although we demonstrated the utility of US complementation with SDAI, we believe that US is not the only important factor and clinical joint examination skills are still critical in this process.

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Increased accuracy in the clinical assessment of joints with US complementation will result in more reliable and valid index determination.

This study has some limitations. The study design analysis was cross sectional, and it was difficult to fully demonstrate utility of the US-adjusted composite measure without assessing follow-up data. In future studies, we will investigate the usefulness of this feasible US-adjusted composite measure over a long-term follow-up period.

We showed the inaccuracy of clinical joint examinations and the utility and validity of US complementation with reduced joints for assessing RA disease activity. Fewer joints used with US complementation can improve the quality of clinical assessments for patients with RA in usual clinical settings.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary material available online