Structural deterioration of finger joints with ultrasonographic synovitis in rheumatoid arthritis patients with clinical low disease activity

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ABSTRACT

Objectives We studied the relations between synovial vascularity (SV) and structural alteration of finger joints in patients with rheumatoid arthritis (RA) and long-term sustained clinical low disease activity (CLDA).

Methods RA patients with CLDA of more than 2 years (minimum 1 year of CLDA for study entry plus 1 year of observation) were analysed. Quantitative SV values were sequentially measured in each finger joint using power Doppler ultrasonography (0, 8th, 20th and 52nd weeks). Radiological progression of local finger joints was evaluated according to Genant-modified Sharp score (0 to 52nd week).

Results Of the 25 patients enrolled, 15 patients were finally analysed after excluding 10 patients who failed to maintain CLDA during the observational period. Changes in radiological progression of metacarpophalangeal and proximal interphalangeal joints with positive SV were significantly greater than those in joints with negative SV. Joint space narrowing (JSN) strongly related to structural alteration of finger joints. In joints with positive SV, changes in structural alteration did not relate to total SV values, which reflect total exposure to inflammation in an observational period.

Conclusions Even in patients with a long period of CLDA, finger joints with positive SV showed structural alteration, especially in the progression of JSN.

Trial registration. University Hospital Medical Information Network Clinical Trials Registry; http://www.umin.ac.jp/ctr/; UMIN000007305

INTRODUCTION

Treat to target (T2T) is an evidence-based therapeutic strategy for rheumatoid arthritis (RA) in which the actual goal is to induce and sustain clinical remission or low disease activity as defined by a scoring system such as the Disease Activity Score with 28 Joints (DAS28) [1]. Although the utility of T2T has been well established, local joints with poor prognosis can exist despite overall clinical improvement in RA [2]. Brown et al. reported that imaging-proven synovitis in RA with sustained clinical remission was related to structural deterioration [3, 4]. According to their observation, they called this low symptomatic joint inflammation “sub-clinical synovitis”, which has received increasing attention in the clinical practice of RA. We established a quantitative measurement of the synovial vascularity (SV) of finger joints using power Doppler ultrasonography and have studied the relation between local SV and joint destruction in RA [5]. We previously reported that existing finger joints with remaining SV during induction and consolidation of clinical low disease activity (CLDA) lead to joint destruction [5, 6]. Furthermore, we found that structural alteration of these joints progresses even at low levels of positive SV [7]. We speculated that this unique joint inflammation might be an early phase of sub-clinical synovitis. In long-term sustained CLDA, finger joints sequentially show various levels of positive SV with minimal clinical symptoms. The relation between SV and joint destruction is unclear in these joints. We therefore focused on and studied this relation with quantitative measurement of ultrasound

SV in each finger joint.

PATIENTS AND METHODS

Study design

We enrolled 25 patients with RA and long-term (>1 year) CLDA (3.2>DAS28-ESR [erythrocyte sedimentation]) in this study (n=25). The treatments were carried out over an observational period of 52 weeks and finally, 15 patients who could sustain CLDA were analysed. Change in the treatments were not allowed throughout the observational period. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

Assessments

Swollen and tender joints were assessed at baseline and at the 8^{th}, 20^{th} and 52^{nd} weeks by rheumatologists (MM, KT) who were blinded to the ultrasonographic results. Blood tests for ESR were performed at each assessment and the DAS28-ESR was calculated [8]. Quantitative measurement of SV was determined by counting the number of vascular flow pixels in the region of interest as was established in a previous report [5]. Joint destruction was assessed according to the Genant-modified Sharp score (SS) by a rheumatologist (JF)

who was blinded to other clinical information [9]. Total SS (TSS) was an index of overall radiological progression comprised of finger, wrist and toe joint scores. We defined finger joints SS (FSS) by summation of finger joint (metacarpophalangeal [MCP] and proximal interphalangeal [PIP]) scores to evaluate individual radiological progression of finger joints.

Ultrasonography and radiography

Ultrasonography was performed at baseline and at the 8^{th}, 20^{th} and 52^{nd} weeks by one of three ultrasound experts (MH, FS, AN) specialised in musculoskeletal ultrasonography who were blinded to other clinical information. A 13-MHz linear array transducer and ultrasonographic machine were used (EUP-L34P, HI VISION Avius; HITACHI, Tokyo, Japan). Power Doppler settings were described previously [5, 6]. The 1^{st} – 5^{th} MCP and 1^{st} – 5^{th} PIP joints were scanned in the longitudinal plane over the dorsal surface. Plain radiographs of hands, wrists and feet were obtained at baseline and at the 52^{nd} week.

Statistical analysis

Differences in parameters were examined using nonparametric tests (Friedman test, Wilcoxon test and Mann-Whitney U test). Categorical data were analysed by Cochran's Q test. Observer reliability of quantitative power Doppler sonography was estimated by intraclass correlation coefficients (ICC). Agreement between two variables was analysed by kappa value (strength

of agreement: <0.2 poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 good, 0.81-1 very good). The smallest detectable change (SDC) in radiographic score was calculated according to a previous study [10]. A value of $P<0.05$ was considered to indicate statical significance. Statical analyses were calculated with the use of the Excel (Microsoft, Redmond, WA), and MedCalc 12.7.5.0 (MedCalc Software, Mariakerke, Belgium) programs.

Results

Clinical assessment

Among the 25 enrolled patients, 8 patients could not maintain CLDA, and 2 patients failed to be followed before the end of the observational period. Thus, 15 patients (age; median=54, range 32-69, sex; female/male 13/2) were finally analysed. The median of duration of disease and CLDA were 50 months (range 26-196) and 15 months (range 12-19), respectively. The patients had been treated with non-biological disease-modified antirheumatic drugs (DMARDs) (8 patients with methotrexate [MTX], 3 patients with MTX + tacrolimus) or with biologics (1 patient with MTX + adalimumab, 2 patients with MTX + tocilizumab [TCZ] and 1 patient with TCZ monotherapy). Six patients were treated with prednisolone (2-6mg/day) maintained throughout the observational period. There were no significant differences in clinical disease activity according to DAS28-ESR for the change through baseline and the 8^{th}, 20^{th} and 52^{nd} weeks (baseline mean=2.03, 8^{th} week 2.17, 20^{th} week 1.65, 52^{nd} week 1.96,

P=0.773). Change of swollen and tender joint counts were shown in supplemental table. Agreement between swollen and/or tender joints and joints with positive SV through observational period were analysed. There was no relation between them (kappa value=0.110). Both of the TSS and FSS significantly increased from baseline to 52nd week (TSS: baseline median=101, 52nd week 105, *P*=0.0001, FSS: baseline median=47, 52nd week 49, *P*=0.0012).

Structural alteration of individual finger joints between joints with positive and negative SV

Changes in local SS (ΔL-SS) of MCP plus PIP joints with positive SV were significantly higher than those with negative SV (Figure 1). The changes in local joint space narrowing score (ΔL-JSN) and erosion score (ΔL-ES) in joints with positive SV were significantly higher than those with negative SV (Figure 1). To analyse which of the two factors ΔL-JSN or ΔL-ES, had more influence on ΔL-SS, the occurrence of the three factors was analysed by Cochran's Q test (Q=43.3, *P*<0.001). The results revealed that ΔL-ES was significantly different from other factors. Regression analysis revealed ΔL-SS to be more strongly related with ΔL-JSN (R^2=0.78, *P*<0.0001) than with ΔL-ES (R^2=0.43, *P*<0.0001).

We next studied each of the MCP and PIP joints. For both of these joints, ΔL-SS of the joints with positive SV was significantly higher than that of the joints with negative SV

(Figure 2). Focusing on joints with positive SV, cumulative SV of each joint relates to the level of exposure to inflammation. We calculated the cumulative SV by summation of the sequential SV value of each joint (sum-SV), (MCP; n=38, median=2580, range 246-22113 and PIP; n=17, median=2703, range 246-26536). These joints were categorised into two groups according to high and low levels of sum-SV divided by the median value. There were no significant differences in ΔL-SS between high and low levels of sum-SV in each of MCP and PIP joints (Figure 2).

Reliability of imaging analysis

Representative ultrasound images for 20 MCP and 20 PIP joints were randomly chosen, and SV was measured 3 times each by the 3 ultrasonographers (MH, FS, AN). The intra-observer ICC were 0.9968-0.9998 for MCP and 0.9984-0.9999 for PIP joints. The inter-observer ICC were 0.9987-0.9994 for MCP and 0.9996-0.9999 for PIP joints. The SDC of ΔL-SS, ΔL-JSN and ΔL-ES were calculated (0.32, 0.23 and 0.25, respectively). None of the calculated SDCs exceeded the smallest unit of scoring (0.5).

DISCUSSION

In this report, we focused on finger joints with positive SV remaining in patients with long-term CLDA. We used quantitative measurement of local SV in each joint. Our study

revealed two main points. First, structural alteration, especially JSN, occurred in joints with positive SV. Second, progression of structural alteration increased irrespective of the level of sum-SV. From these results, we emphasise that joints may be at risk for structural alteration even with sustained CLDA and a low level of positive SV in each joint.

Considering the first point, it appears that ultrasonographic synovitis can maintain destructive power in joints with positive SV even in periods of CLDA. Such synovitis is termed sub-clinical synovitis and shows no or minimal clinical symptoms. In this study, ultrasonographic synovitis with positive SV were compatible with sub-clinical synovitis. Our results showed that JSN was more affected by sub-clinical synovitis than by bone erosion. It could be speculated that sub-clinical synovitis was not potent enough to invade bone regions, but it could harm cartilage/tendons resulting in JSN. JSN could directly influence the range of motion and ultimately affect joint function, thus being very important clinically. Considering the second point, SV originally reflects a level of joint inflammation. Hence, time-integrated SV correlates with the progression of joint destruction; however, our results conflict with this theory. We previously reported that the relation between SV and joint destruction during induction and soon after achieving CLDA showed unique results similar to those obtained in the present study [7]. These results indicate that the synovitis may alter inflammation outcome in a heterogeneous way after a long duration. It was previously reported that a low level of ultrasonographic abnormality may be of little importance after achieving clinical

improvement [11]. Our results appear to contradict those of the previous report by showing that significant joint destruction can occur even after obtaining clinical improvement of long duration. More studies are necessary to examine this controversy.

The major limitations of this study were that it was a small-scale single-centre study with a short observational time. Our results must be confirmed by a large-scale multi-centre study. Another limitation was uniformity of treatments in the study. Ikeda et al. reported that clinical implications of SV may change depending on whether non-biological DMARDs or biologics are administered [12]. In daily clinical practice, we clinicians frequently encounter joints with positive SV in patients with CLDA. We shed light on the nature of these joints by quantitative measurement of local SV and found that simple dichotomic judgment of SV could predict joint prognosis. Our results may be utilised in daily clinical practice and may provide some encouragement to practice "true" T2T. There is an ongoing study of RA outcome called the Targeted Ultrasound Initiative in which the treatment target is based on ultrasound joint abnormalities [13]. Taken together with our findings, a combination of clinical and ultrasound criteria may be useful and give benefit to the clinical practice of RA.

Key messages

Destruction occurred in joints with positive SV remaining in patients with long-term CLDA.

Joints may be at risk for destruction even with a low level of positive SV.

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Figure legends

Figure 1. Changes in radiological progression between metacarpophalangeal plus proximal interphalangeal finger joints with positive and negative synovial vascularity (SV). Change in local Genant-modified Sharp score (ΔL-SS) (A), local joint space narrowing (ΔL-JSN) (B) and local erosion score (ΔL-ES) (C) between joints with positive (+) and negative (-) SV are shown.

Figure 2. Changes in local Genant-modified Sharp score (ΔL-SS) between metacarpophalangeal (MCP) and proximal interphalangeal (PIP) finger joints with positive and negative synovial vascularity (SV) and detailed analysis of joints with positive SV. Graphs for MCP joints (A, C) and PIP joints (B, D) are shown. The ΔL-SS of joints with positive (+) and negative (-) SV are shown in panels A and B. The ΔL-SS of joints with a low (L-group) and high (H-group) sum of SV values are shown in panels C and D.

Figure 1.

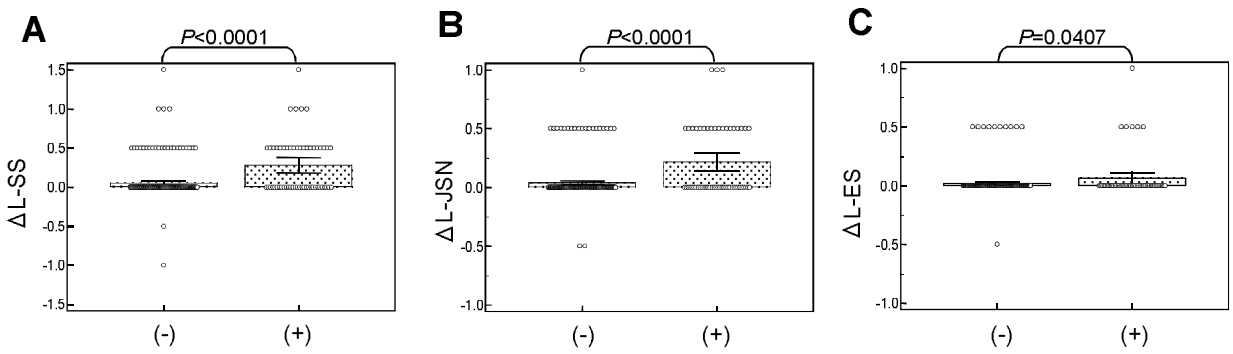
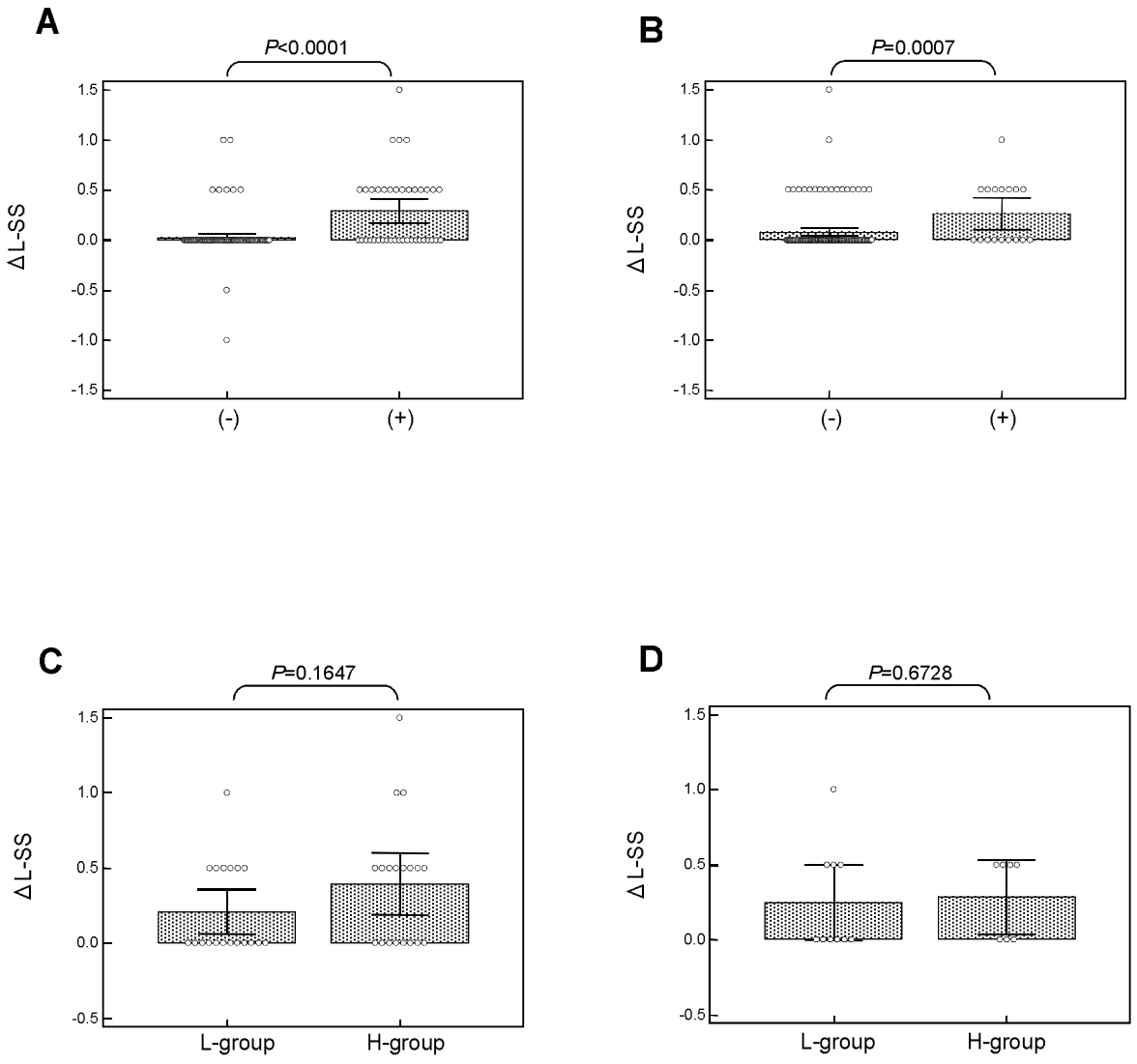

A
P<0.0001
ΔL-SS
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
(-)
(+)
B
P<0.0001
ΔL-JSN
1.0
0.5
0.0
-0.5
-1.0
(-)
(+)
C
P=0.0407
ΔL-ES
1.0
0.5
0.0
-0.5
-1.0
(-)
(+)

Figure 2.


A
P<0.0001
ΔL-SS
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
(-)
(+)
B
P=0.0007
ΔL-SS
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
(-)
(+)
C
P=0.1647
ΔL-SS
1.5
1.0
0.5
0.0
-0.5
L-group
H-group
D
P=0.6728
ΔL-SS
1.5
1.0
0.5
0.0
-0.5
L-group
H-group