CLINICAL AND ULTRASOUND ANKLE INVOLVEMENT IN RHEUMATOID ARTHRITIS IN REMISSION

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Abstract

Objective. We aimed to evaluate the prevalence and differences of clinical and ultrasound involvement of ankles in rheumatoid arthritis (RA) patients in remission.

Methods. RA patients were recruited in 2018 in the random order of presentation from the out-patient clinic. In the day of enrolment, all patients underwent clinical examination (by a senior rheumatologist, blind to other evaluations), inflammatory markers (e.g. C-reactive protein – CRP) and ankle ultrasound (performed and interpreted by a single rheumatologist with more than 7 years of experience).

Results. The sample included 59 patients in DAS28CRP remission, 27 in SDAI remission and 20 in Boolean remission. Among these 3 categories of remission, overall clinical ankle involvement presented similar prevalence (revolving around 30%). On average, 77% of patients presented overall ultrasound ankle involvement among the 3 categories of remission, with similar frequencies of ankle joint synovial hypertrophy (SH; 33%), power Doppler (PD) positive joint SH (15%), ankle joint effusion (60%), ankle tenosynovitis (27%) and PD positive ankle tenosynovitis (15%). In the subgroup of RA patients in DAS28CRP remission, compared to patients without clinical or ultrasound ankle involvement, those with at least one involved ankle had a significantly higher median CRP (0.34 mg/dl versus 0.19 mg/dl, p = 0.042).

Conclusion. Among RA patients in remission, regardless of its definition, clinical and ultrasound involvement of ankles is frequent. Clinical and ultrasound screening of ankles in RA patients in remission seems an appropriate strategy.

Keywords: ankle, ultrasound involvement, rheumatoid arthritis, remission

List of text abbreviations

ACPA – anti-citrullinated protein antibodies
ACR – American College of Rheumatology
CRP – C-reactive protein
DAS – disease activity score
ESR – erythrocyte sedimentation rate
EULAR – European Leagues against Rheumatism
HAQ – health assessment questionnaire
MRI – magnetic resonance imaging

INTRODUCTION

Treatment of rheumatoid arthritis (RA) should aim at sustained remission in every patient (1), an ideal which is rare in real-life settings (2). Unfortunately, there is no consensus on what “sustained” should mean in terms of time and there is debate over the proper definition of “remission” (3), regarding the appropriate composite score (4,5), its components (6), its best threshold for remission (7) and whether to include synovial imaging information (8). Since low baseline disease activity is a significant predictor of remission (9), the true problem is how to assess disease activity. Imaging of joints and
tendons is a feasible choice. In patients with DAS28-defined remission, ultrasound is able to detect grey scale synovial hypertrophy (SH) (10) and positive power Doppler (PD) synovitis and tenosynovitis both in joints included in the clinical evaluation of composite scores (11-21) and also in the excluded joints, such as the ankles (22,23) and feet (24-31), regardless of treatment type (32). Convincing literature evidence shows that there is a quantitative positive relationship between remission and residual ultrasound activity. On one hand, the lack of ultrasound activity predicts achievement and persistence of remission (33,34). On the other hand, there is a very high degree of confidence that residual synovial activity is a significant predictor for loss of remission (relapse, flare) and radiographic progression since controlled studies (35-37), meta-analyses (38,39), magnetic resonance imaging (MRI) studies (40-46), biological markers (14) and histology (47,48) have confirmed the cited ultrasound observations. The loss of remission tends to happen in the first year of follow-up (39), especially if treatment is withdrawn (49,50). Despite this, ultrasound screening of residual activity in remission focuses on the hands (51-53), excluding the ankles, just as DAS28 did for clinical evaluation. In this context, we aimed to evaluate the prevalence and differences of clinical and ultrasound involvement of ankles in RA patients in remission. The group of RA patients in remission represent a sub-group of a larger sample of RA patients enrolled to evaluate the frequency and correlation of ankle ultrasound inflammatory lesions with MRI and disease activity (results under publication).

**METHODS**

**Patient selection**

RA patients fulfilling the 2010 American College of Rheumatology (ACR)/European Leagues against Rheumatism (EULAR) RA classification criteria (54) were recruited in 2018 in the random order of presentation to the out-patient clinic. Exclusion criteria consisted of age below 18 years, history or current ankle deformity/surgery, local complex regional pain syndrome, fibromyalgia, pregnancy, injectable glucocorticoids (pulse-therapy, intra-articular injections) in the month prior to study inclusion. Medication which can influence ultrasound finding was allowed as follows: oral glucocorticoids, if less than 10 mg prednisone equivalent per day and stable in the prior month; non-steroidal anti-inflammatory drugs (NSAIDs) if stable in the prior week. The study was approved by the local ethics committee and all patients gave written informed consent. In the day of enrolment, all patients underwent clinical examination, laboratory tests and ankle ultrasound, reported global assessment of general health (PtGA; on a 0-10 scale) and completed independently the health assessment questionnaire (HAQ).

**Clinical and laboratory evaluation**

All clinical examinations were done by the same senior rheumatologist, blinded to laboratory and ultrasound results. A clinical interview noted aspects of general medical history, RA history and current anti-rheumatic treatment (55). Standard 28 tender/swollen joint counts (T/SJC) were performed and disease activity scores were computed: DAS28 (56) using C-reactive protein (CRP; which is better correlated with synovial inflammation than erythrocyte sedimentation rate – ESR (57)) and SDAI (simplified disease activity index) (58). Remission was defined using either cut-offs of composite score (DAS28 < 2.6 or SDAI ≤ 3.3) or the Boolean approach (TJC ≤ 1, SJC ≤ 1, PtGA ≤ 1 and C-reactive protein, CRP ≤ 1 mg/dl) (3). Additionally, both ankles were examined for signs of inflammation (pain and/or swelling). Laboratory tests included CRP (normal < 0.5 mg/dl), ESR (normal < 20 mm/h), rheumatoid factor (RF; normal < 30 IU/ml) and anti-citrullinated protein antibodies (ACPA; normal < 20 IU/ml).

**Musculoskeletal ultrasound**

All ultrasound examinations were performed and interpreted by a single rheumatologist with more than 7 years of experience, using an Esaote MyLabTwice machine (12-18 MHz linear transducer). Both ankles were scanned first in grey scale in order to detect inflammatory lesions, and then PD technique was used to evaluate intra- and peri-articular vascularity, using constant settings (gain just below the noise level, 750 Hz pulse repetition frequency, 8-10 MHz Doppler frequency, low wall filter). Ankle assessment was done according to the EULAR-recommended ankle technique (59). Three ankle joins (tibiotalar with anterior and posterior recess, talonaviculair and subtalar joint from medial, lateral and posterior aspects) and 8 ankle tendons (tibialis anterior, extensor hallucis longus, extensor
digitorum longus, tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus longus, peroneus brevis) were evaluated. The following pathological findings were recorded: joint SH, joint effusion and tenosynovitis. Their interpretation was done according to OMERACT recommendations (60). In order to quantify joint SH and PD, we used the initial semi-quantitative scale developed by Szkudlarek et al. (61,62), taking into account the latest EULAR-OMERACT recommendations (63). For joint effusion, we a dichotomous score (present, absent). Multiple window ultrasound evaluation of the same joint recorded the highest SH/PD grade (0-3 corresponding to “absent”, “minimal”, “moderate” and “severe”). For tenosynovitis quantification, we applied the OMERACT recommended score (64).

Statistics

Distribution normality was assessed using descriptive statistics, normality and stem-and-leaf plots, and Kolmogorov-Smirnov tests. Differences of continuous variables (e.g. age) among categorical variables (e.g. clinical ankle involvement) were tested with non-parametric tests for independent variables (Mann-Whitney tests). Associations of two dichotomous variables (e.g. ultrasound involvement and RF positivity) were studies with χ² tests. The statistical tests were considered significant if p < 0.05 and were computed with IBM SPSS Statistics version 22.0 for Windows (Armonk, NY, IBM Corp.).

RESULTS

The sample included 183 RA patients in different degrees of disease activity. For the purpose of this sub-analysis, only patients in remission were retained from the 183 total sample: 59 (32.2%) in DAS28_CRP remission, 27 (14.8%) in SDAI remission and 20 (10.9%) in Boolean remission. Among these 3 categories of remission (Table 1), overall clinical ankle involvement presented similar prevalence (revolving around 30%), with discrepant frequencies of tender and swollen ankles (there were no swollen ankles in Boolean remission, while a tenth of patients in DAS28_CRP remission had at least one swollen ankle). On average, 77% of patients presented overall ultrasound ankle involvement among the 3 categories of remission, with similar frequencies of B-mode ankle joint SH (33%), positive PD joint SH (15%), ankle joint effusion (60%), B-mode ankle tenosynovitis (27%) and positive PD ankle tenosynovitis (15%) regardless of remission definition. Overall, 22% of patients had positive PD in ankle joints or tendons in each category of remission definition. True remission, defined as normal ankles at clinical examination and the lack of abnormal ultrasound findings, was observed in 18.6% of patients in DAS28_CRP remission, 20.0% in patients in Boolean remission and 25.9% in patients in SDAI remission (Table 1).

In contrast to the SDAI and Boolean remission subgroups, the subgroup of RA patients in DAS28_CRP remission was large enough to assess differences and associations with clinical and laboratory variables (Table 2). This subgroup consisted mainly of women (88.1%) with a median of 52 years of age and 9 years of disease duration, with low frequency of positive auto-immune serology (54.2% RF positive and 66.1% ACPA positive) and high frequency of anti-rheumatic treatment (91.5% were on conventional synthetic anti-rheumatic drugs and 52.5% on biologics). The most frequent SH was detected in talonavicular joints (18.6%), while the most frequent tenosynovitis was detected in tibialis posterior tendons (18.6%). Regarding SH grading in either ankle, 17.0% had grade 1, 15.3% grade 2 and 3.4% grade 3. Similarly, regarding tenosynovitis grading in either ankle, 11.9% had grade 1, 11.9% grade 2 and 3.4% grade 3. Compared to patients without clinical ankle involvement, those with at least one tender or swollen ankle had a significantly higher median CRP (0.34 mg/dl versus 0.19 mg/dl, p = 0.042; Figure 1) and significantly higher prevalence of pathologic ultrasound findings (Table 3). Significantly higher median CRP values were observed when comparing patients with and without ankle joint SH, positive PD ankle joint SH and positive PD ankle tenosynovitis (Figure 1). Representative ultrasound images of B-mode and positive PD SH and tenosynovitis are shown in Figure 2.

DISCUSSION

In summary, we observed a high frequency of clinical and ultrasound involvement of ankles in RA patients in remission, regardless of its definition. Our data have shown that CRP is a marker of this residual activity. Although other studies have evaluated ankle joints in RA patients in remission, the study aims were different and therefore there is little information reported individually for clinical and ultrasound ankle involvement. For example, Son et al.
TABLE 1. Prevalence of clinical and ultrasound (US) findings among RA patients in remission

| remission defined by | DAS28<sub>CRP</sub> (n = 59) | SDAI (n = 27) | Boolean (n = 20) |
|----------------------|--------------------------|----------------|-----------------|
| = 1 tender ankle     | 18 (30.5%)               | 8 (29.6%)      | 6 (30.0%)       |
| = 1 swollen ankle    | 6 (10.2%)                | 1 (3.7%)       | 0 (0%)          |
| clinical ankle involvement | 19 (32.8%)             | 8 (29.6%)      | 6 (30.0%)       |
| ankle joint SH<sup>‡</sup> | 21 (35.6%)             | 8 (29.6%)      | 7 (35.0%)       |
| positive PD joint SH<sup>‡</sup> | 10 (16.9%)             | 4 (14.8%)      | 3 (15.0%)       |
| ankle joint effusion<sup>‡</sup> | 35 (59.3%)             | 15 (55.6%)     | 13 (65.0%)      |
| ankle TS<sup>§</sup> | 16 (27.1%)               | 8 (29.6%)      | 5 (25.0%)       |
| positive PD TS<sup>§</sup> | 9 (15.3%)               | 4 (14.8%)      | 3 (15.0%)       |
| positive PD<sup>‡</sup> | 14 (23.7%)               | 6 (22.2%)      | 4 (20.0%)       |
| US ankle involvement<sup>‡</sup> | 46 (78.0%)             | 20 (74.1%)     | 16 (80.0%)      |
| true remission<sup>‡</sup> | 11 (18.6%)               | 7 (25.9%)      | 4 (20.0%)       |

- variables are reported as "count (percentage of subgroup)"; * defined as at least one right or left tender or swollen ankle; # SH/PD/effusion detected by US in either right or left TJJ, TNJ or STJ; & TS/PD detected by US in either right or left ankle tendons (TA, EHL, EDL, PL, PB, TP, FDL, FHL); ¶ PD detected by US in either right or left ankle joints (TJJ, TNJ or STJ) or tendons (TA, EHL, EDL, PL, PB, TP, FDL, FHL); ¥ defined as either SH and/or TS detected by US in either right or left ankle joints (TJJ, TNJ, STJ) or tendons (TA, EHL, EDL, PL, PB, TP, FDL, FHL); ‡ defined as normal ankles at clinical examination and no SH, TS and PD on US.

CRP - C-reactive protein; DAS - disease activity score; EHL - extensor hallucis longus; EHL - flexor digitorum longus; FDL - flexor digitorum longus; FHL - flexor hallucis longus; PB - peroneus brevis; PD - power Doppler; PL - peroneus longus; SDAI - simplified disease activity index; SH - synovial hypertrophy; STJ - subtalar joint; TA - tibialis anterior; TNJ - talonavicular joint; TP - tibialis posterior; TS - tenosynovitis; TJJ - talocalcaneal joint.

TABLE 2. Comparison of RA patients in DAS28<sub>CRP</sub> remission according to type of ankle involvement

| type of ankle involvement | clinical | ultrasound |
|---------------------------|----------|------------|
| all (n = 59)              |          |            |
| women                     | 52 (88.1%) | 35 (57.5%) |
| age (y)                   | 58 (20)   | 59 (19)    |
| RA duration (y)           | 9 (15)    | 12 (15)    |
| NSAIDs                    | 8 (13.6%) | 6 (15.0%)  |
| glucocorticoids           | 9 (15.3%) | 6 (15.0%)  |
| csDMARDs                  | 54 (91.5%)| 36 (90.0%) |
| bDMARDs                   | 31 (52.9%)| 23 (57.5%) |
| RF (IU/mL)                | 46 (139)  | 41 (119)   |
| RP positive               | 32 (54.2%)| 21 (52.6%) |
| ACPA (IU/mL)              | 141 (212) | 137 (217)  |
| ACPA positive             | 39 (66.1%)| 25 (62.5%) |
| TJC28                     | 0 (1)     | 0 (1)      |
| SJC28                     | 0 (0)     | 0 (0)      |
| ESR (mm/h)                | 21 (18)   | 22 (16)    |
| CRP (mg/dL)               | 0.26 (0.32)| 0.19 (0.29)| 0.34 (0.47) |
| PtGA (mm)                 | 20 (14)   | 17 (10)    |
| PhGA (mm)                 | 10 (11)   | 10 (3)     |
| HAQ                       | 0.6 (1.1) | 0.8 (1.4)  |

- differences between subgroups (clinical, ultrasound) were assessed with χ² tests for nominal variables (e.g. RF positive) and Mann Whitney tests for continuous variables (e.g. RF titre); * non-significant; ¶ p = 0.042; & p = 0.013
- ACPA - anti-citrullinated protein antibodies; csDMARDs - biologic/conventional synthetic disease-modifying anti-rheumatic drugs; CRP - C-reactive protein; DAS - disease activity score; ESR - erythrocyte sedimentation rate; HAQ - health assessment questionnaire; IU - international units; NSAIDs - non-steroidal anti-inflammatory drugs; PhGA - physician/patient global assessment of disease activity; RA - rheumatoid arthritis; RF - rheumatoid factor; S/TJC - swollen/tender joint count; y - years
reported that 25% of their RA patients in DAS28 remission had ankle/foot joint swelling, and 81% of them had ankle/foot tenderness, without ultrasound data. In our study, only the stringent Boolean definition of RA achieved 0% prevalence of swollen ankles, but nonetheless it had a 15% prevalence of positive PD SH and 15% prevalence of positive PD tenosynovitis. In this context, the observations of our study can be interpreted in two ways: either the definition of remission is loose, or treatment strategy/molecules are insufficient to control RA synovitis (a scenario not suited for our current study, since it should discuss the definition of remission and the need for new treatment targets). In the first scenario, the reasonable consequence would be to add ankles to composite scores and to their definition of remission. This possibility has been explored by previous researchers who reported that composite scores us-

### TABLE 3. Comparison of ultrasound findings in symptomatic and asymptomatic patients in DAS28_{CRP} defined remission (n = 59)

|                  | Clinical examination of ankles | Clinical examination of ankles |
|------------------|-------------------------------|-------------------------------|
|                  | normal (n = 40)               | swollen (n = 19)              | p       |
| joint SH*        | 9 (22.5%)                     | 12 (63.2%)                    | 0.002   |
| positive PD SH+  | 2 (5.0%)                      | 8 (42.1%)                     | <0.001  |
| tenosynovitis+   | 7 (17.5%)                     | 9 (47.4%)                     | 0.016   |
| positive PD tenosynovitis+ | 2 (5.0%) | 7 (36.8%)                     | 0.001   |
| positive PD*     | 4 (10.0%)                     | 10 (52.6%)                    | <0.001  |

Notes: variables are reported as # SH/PD: effusion detected by ultrasound in either right or left TTJ, TNJ or STJ; p values represent the significance level of χ² tests; & tenosynovitis/PD detected by ultrasound in either right or left ankle tendons (TA, EHL, EDL, PL, PB, TP, FDL, FHL); § PD detected by ultrasound in either right or left ankle joints (TTJ, TNJ or STJ) or tendons (TA, EHL, EDL, PL, PB, TP, FDL or FHL).

Abbreviations: CRP – C-reactive protein; DAS – disease activity score; EDL – extensor digitorum longus; EHL – extensor hallucis longus; FDL – flexor digitorum longus; FHL – flexor hallucis longus; PB – peroneus brevis; PD – power Doppler; PL – peroneus longus; SH – synovial hypertrophy; STJ – subtalar joint; TA – tibialis anterior; TNJ – talonavicular joint; TP – tibialis posterior; TTJ – tibiotalar joint.

### FIGURE 1. Median CRP levels according to type of ultrasound ankle findings: ankle joint SH (left; defined as SH detected by ultrasound in either right or left TTJ, TNJ or STJ), PD+ ankle joint (defined as PD detected by ultrasound in either right or left TTJ, TNJ or STJ) and PD+ ankle TS (defined as PD detected by ultrasound in either right or left TA, EHL, EDL, PL, PB, TP, FDL or FHL tendons). Differences tested with Mann Whitney tests:

* p = 0.015; # p = 0.038; & p = 0.037. CRP is reported as square root for illustration purposes. CRP – C-reactive protein; PD+ – positive power Doppler; SH – synovial hypertrophy; TS – tenosynovitis.
ing 28 joint counts have similar performance in evaluating disease activity with or without ankles and feet (66). Also, long-term radiological and functional outcomes are predicted similarly by remission defined using the standard 28 joint count or extended 38 joint count (including ankles) (29). However, the ankles seem to be a good place to screen for residual activity in RA remission since Naredo et al. proved that a model of ultrasound examination including ankles had high sensitivity for detection of residual activity in remission (22), and it was a significant predictor of unstable remission (23). From the evidence presented above, it would seem redundant the change the current composite score by adding ankles, but examining ankles in patients in remission would qualify as good clinical practice (3). The clin-
tical question is whether clinical/ultrasound ankle involvement should be an argument to change treatment of RA patients in remission. If any of the ankles present with tenderness/swelling and ultrasound confirms an underlying inflammatory lesion, in the absence of other causes for local clinical manifestations, the clinician should take into consideration, in agreement with the patient, setting a more stringent remission definition (such as the Boolean definition) or to aim simply at remitting ankle RA activity. We would expect PtGA to have a bigger weight in taking this decision. There is good evidence to support this initiative: meta-analysis data show that the risk of relapse/flare is 3.2 higher in patients in remission in the presence of positive PD SH (38). Meta-analysis has also shown that the presence of positive PD signals also increase by at least 9 times the risk of radiological progression in individual patients (38,39). There are probably few clinicians who use or call for ultrasound to screen RA patients in remission for active residual synovial activity, especially in the ankles. Given that no more than half of patients achieve point remission in clinical practice (67), the achievement of DAS28-defined remission is rewarding for both patient and rheumatologist. Over the past few years, many ultrasound monitoring scores (68), including for patients in remission (22), have been described and even validated, but there is still no consensus in this direction (it is not yet clear how many joints to scan, which of and what pathological lesions should be included). The usefulness of ultrasound is clearly demonstrated for early diagnosis of disease (54), along with clinical and laboratory parameters. Perhaps the same direction should be followed, namely, disease activity monitoring using composite indices which also include clinical, labora-

ratory and ultrasound parameters. The attempts so far have not been successful because of the low sensitivity to change and difficulties in performing them in daily practice (69,70).

Further research should address the usefulness and feasibility of such ultrasound screening of RA patients in remission with the ultimate purpose to target ankle remission in selected patients.

An important methodological advantage of our study is that ultrasound involvement was defined with both intra-articular (SH) and peri-articular (tenosynovitis) inflammatory findings (most ultrasound scores did not include tenosynovitis). However, there are some limitations which can influence the interpretation of our results: the relatively small sample size of RA patients in remission, the cross sectional design which did not allow to follow the disease evolution, the lack of an ultrasound inter-observer study, the fact that clinical examination was not done individually at the level of each ankle structure (joint, tendon) and the fact that bone damage (erosions) was not evaluated neither by conventional radiography nor ultrasound.

CONCLUSION

Among RA patients in remission, regardless of its definition, a third present clinical ankle involvement (at least one tender/swollen ankle at clinical examination) and 22% present ultrasound positive PD SH or tenosynovitis, changes which are reflected by significantly higher CRP levels. In this context, clinical and ultrasound screening of ankles in RA patients in remission seems an appropriate strategy, taking into account the destructive potential of PR that determines, particularly at this level, a severe functional deficit.

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