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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
NSAIDs – non-steroidal anti-inflammatory drugs
PD – power Doppler
PtGA – patient global assessment of general health
RA – rheumatoid arthritis
RF – rheumatoid factor
SJC – swollen joint count
SH – synovial hypertrophy
TJC – tender joint counts

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

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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 bellow 18 years, history or current ankle deformity/surgery, local complex regional pain syndrome, fibromyalgia, pregnancy, injectable glucocorticoids (pulse-therapy, intramuscular, 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, talonavicular 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 χ^2 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		
	$DAS28_{CRP}$ *(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[#]	21 (35.6%)	8 (29.6%)	7 (35.0%)
positive PD joint SH[#]	10 (16.9%)	4 (14.8%)	3 (15.0%)
ankle joint effusion[#]	35 (59.3%)	15 (55.6%)	13 (65.0%)
ankle TS[&]	16 (27.1%)	8 (29.6%)	5 (25.0%)
positive PD TS[&]	9 (15.3%)	4 (14.8%)	3 (15.0%)
positive PD[§]	14 (23.7%)	6 (22.2%)	4 (20.0%)
US ankle involvement[¶]	*46 (78.0%)*	*20 (74.1%)*	*16 (80.0%)*
true remission[‡]	*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 TTJ, 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 (TTJ, TNJ or STJ) or tendons (TA, EHL, EDL, PL, PB, TP, FDL or FHL); ¶ defined as either SH and/or TS detected by US in either right or left ankle joints (TTJ, 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; 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; SDAI-simplified disease activity index; SH-synovial hypertrophy; STJ-subtalar joint; TA-tibialis anterior; TNJ-talonavicular joint; TP-tibialis posterior; TS-tenosynovitis; TTJ-tibiotalar joint.

TABLE 2. *Comparison of RA patients in $DAS28_{CRP}$ remission according tu type of ankle involvemet*

		type of ankle involvement			
		clinical		*ultrasound*	
	all (n = 59)	no (n = 40)	yes (n = 19)	no (n = 13)	yes (n = 46)
women	52 (88.1%)	35 (87.5%)	17 (89.5%)[*]	11 (84.6%)	41 (89.1%)[*]
age (y)	58 (20)	59 (19)	57 (21)[*]	58 (25)	59 (19)[*]
RA duration (y)	9 (15)	12 (15)	8 (9)[*]	10 (16)	9 (14)[*]
NSAIDs	8 (13.6%)	6 (15.0%)	2 (11.1%)[*]	1 (7.7%)	7 (15.6%)[*]
glucocorticoids	9 (15.3%)	6 (15.0%)	3 (15.8%)[*]	1 (7.7%)	8 (17.4%)[*]
csDMARDs	54 (91.5%)	36 (90.0%)	18 (94.7%)[*]	12 (92.3%)	42 (91.3%)[*]
bDMARDs	31 (52.5%)	23 (57.5%)	8 (42.1%)[*]	6 (46.2%)	25 (54.3%)[*]
RF (IU/mL)	46 (139)	41 (119)	76 (230)[*]	117 (75)	35 (153)[*]
RF positive	32 (54.2%)	21 (52.5%)	11 (57,9%)[*]	11 (84.6%)	21 (45.7%)[&]
ACPA (IU/mL)	141 (212)	137 (217)	145 (190)[*]	176 (176)	105 (190)[*]
ACPA positive	39 (66.1%)	25 (62.5%)	14 (73.7%)[*]	11 (84.6%)	28 (60.9%)[*]
TJC28	0 (1)	0 (1)	0 (0)[*]	0 (1)	0 (0)[*]
SJC28	0 (0)	0 (0)	0 (0)[*]	0 (0)	0 (0)[*]
ESR (mm/h)	21 (18)	22 (16)	18 (19)[*]	16 (23)	22 (18)[*]
CRP (mg/dL)	0.26 (0.32)	0.19 (0.29)	0.34 (0.47)[#]	0.16 (0.20)	0.27 (0.50)[*]
PtGA (mm)	20 (14)	17 (10)	20 (24)[*]	20 (20)	17 (12)[*]
PhGA (mm)	10 (11)	10 (3)	10 (27)[*]	10 (9)	12 (15)[*]
HAQ	0.6 (1.1)	0.8 (1.4)	0.6 (1.0)[*]	1.4 (1.6)	0.5 (0.9)[*]

- differences between subgroups (clinical, ultrasound) were assessed with χ^2 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; b/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; Ph/tGA - physician/patient global assessment of disease activity; RA – rheumatoid arthritis; RF - rheumatoid factor; S/TJC - swollen/tender joint count; y - years.

TABLE 3. *Comparison of ultrasound findings in symptomatic and asymptomatic patients in DAS28$_{CRP}$- defined remission (n = 59)*

	clinical examination of ankles		
	normal (n = 40)	*= 1 tender/swollen (n = 19)*	p
joint SH[#]	9 (22.5%)	12 (63.2%)	0.002
positive PD joint 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 χ^2 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.

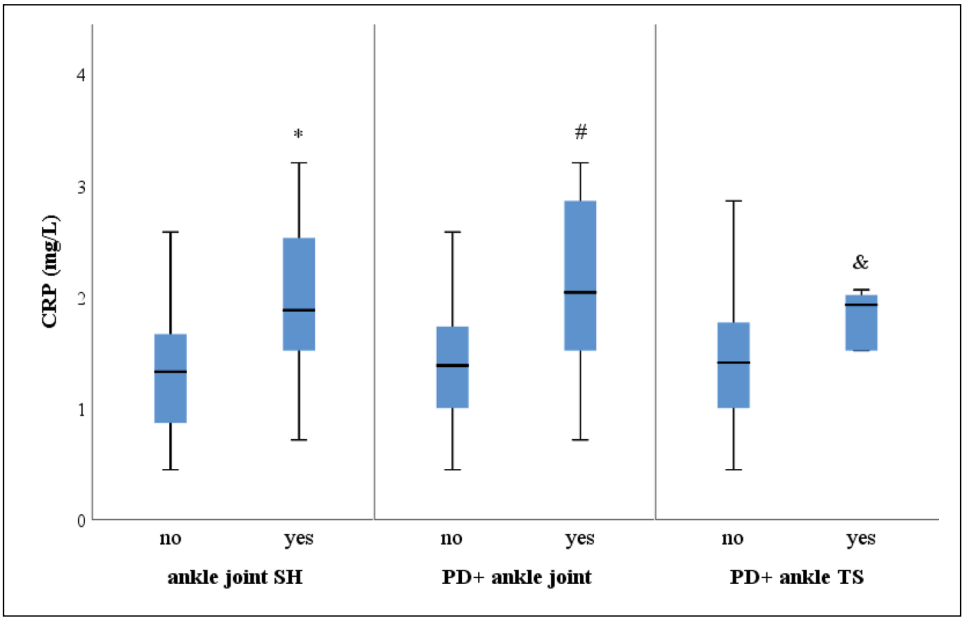

FIGURE 1. *Median CRP levels according to type of ultrasound ankle findings: ankle joint SH (left; defined as SH detected by ultrasound in either right or left TTJ, TNJ or STJ), PD+ ankle joint (defined as PD detected by ultrasound in either right or left TTJ, TNJ or STJ) and PD+ ankle TS (defined as 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.*

(65) 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-

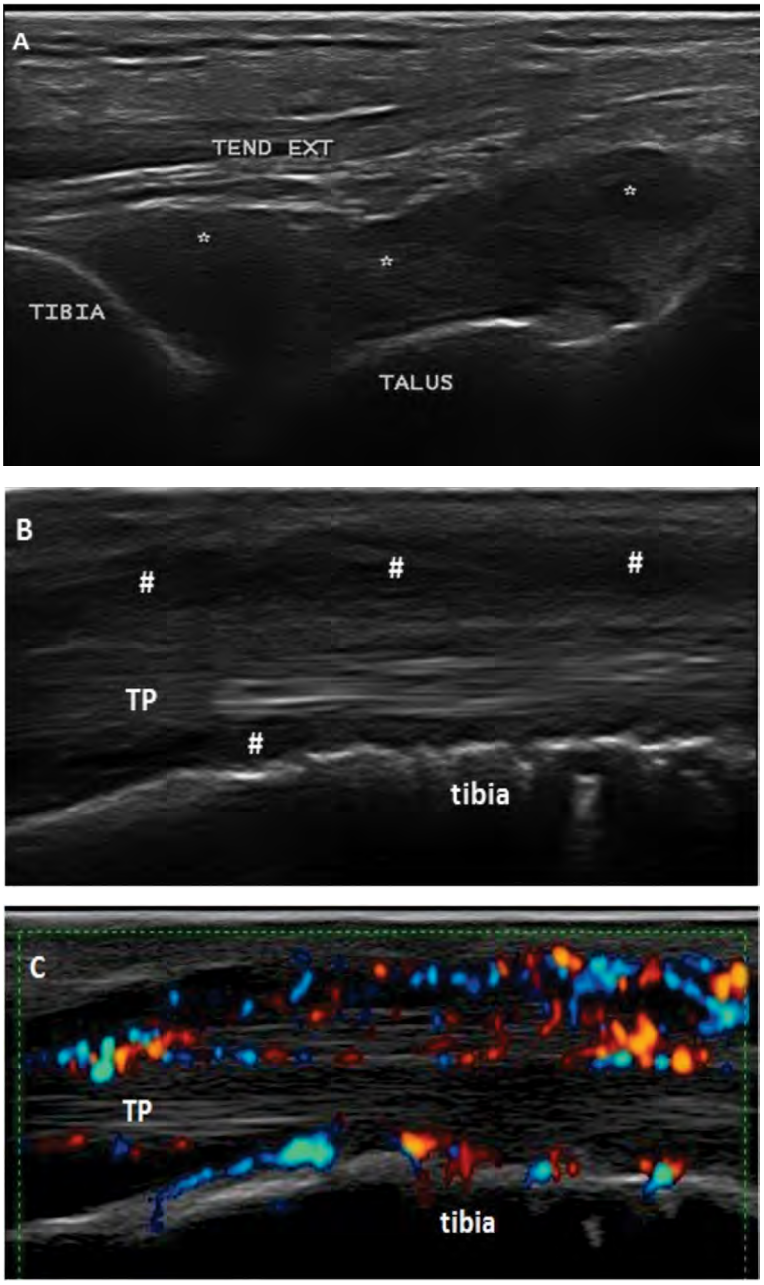

***FIGURE 2**. Ankle ultrasound in a rheumatoid arthritis patient in remission: A) dorsal longitudinal scan of the tibiotalar joint, showing distension of the joint capsule by synovial hypertrophy (*); B) longitudinal scan of the tibialis posterior tendon showing B-mode tenosynovitis (# synovial hypertrophy within the tendon sheath); C) power Doppler mode of the tendon from image B, revealing power Doppler signal both within the synovial sheath and also inside the tendon (TP – tibialis posterior tendon).*

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-

ical 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, laboratory 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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REFERENCES

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis.* 2017;76(6):960-77.
2. de Punder YM, Fransen J, Kievit W, Houtman PM, Visser H, van de Laar MA et al. The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatology* (Oxford). 2012;51(9):1610-7.
3. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis.* 2011;70(3):404-13.
4. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. *Rheumatology* (Oxford). 2010;49(4):683-90.
5. Lee YC, Cui J, Lu B, Frits ML, Iannaccone CK, Shadick NA et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther.* 2011;13(3):R83.
6. Aletaha D, Alasti F, Smolen JS. Rheumatoid arthritis near remission: clinical rather than laboratory inflammation is associated with radiographic progression. *Ann Rheum Dis.* 2011;70(11):1975-80.
7. Sheehy C, Evans V, Hasthorpe H, Mukhtyar C. Revising DAS28 scores for remission in rheumatoid arthritis. *Clin Rheumatol.* 2014;33(2):269-72.

8. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. *Ann Rheum Dis.* 2011;70(5):792-8.
9. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. *Arthritis Care Res* (Hoboken). 2010; 62(8):1128-43.
10. Zufferey P, Moller B, Brulhart L, Tamborrini G, Scherer A, Finckh A et al. Persistence of ultrasound synovitis in patients with rheumatoid arthritis fulfilling the DAS28 and/or the new ACR/EULAR RA remission definitions: results of an observational cohort study. *Joint Bone Spine.* 2014; 81(5):426-32.
11. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. *Mod Rheumatol.* 2013; 23(3):456-65.
12. Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM et al. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis – a systematic review of the literature. *Arthritis Res Ther.* 2013; 15(1):R4.
13. Gartner M, Mandl P, Radner H, Supp G, Machold KP, Aletaha D et al. Sonographic joint assessment in rheumatoid arthritis: associations with clinical joint assessment during a state of remission. *Arthritis Rheum.* 2013; 65(8):2005-14.
14. Ramirez J, Ruiz-Esquide V, Pomes I, Celis R, Cuervo A, Hernandez MV et al. Patients with rheumatoid arthritis in clinical remission and ultrasound-defined active synovitis exhibit higher disease activity and increased serum levels of angiogenic biomarkers. *Arthritis Res Ther.* 2014; 16(1):R5.
15. Geng Y, Han J, Deng X, Zhang Z. Presence of power Doppler synovitis in rheumatoid arthritis patients with synthetic and/or biological disease-modifying anti-rheumatic drug-induced clinical remission: experience from a Chinese cohort. *Clin Rheumatol.* 2014; 33(8):1061-6.
16. Gartner M, Alasti F, Supp G, Mandl P, Smolen JS, Aletaha D. Persistence of subclinical sonographic joint activity in rheumatoid arthritis in sustained clinical remission. *Ann Rheum Dis.* 2015; 74(11):2050-3.
17. Bellis E, Scire CA, Carrara G, Adinolfi A, Batticciotto A, Bortoluzzi A et al. Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the Italian Society for Rheumatology. *Rheumatology* (Oxford). 2016; 55(10):1826-36.
18. Ventura-Rios L, Sanchez Bringas G, Hernandez-Diaz C, Cruz-Arenas E, Burgos-Vargas R. Subclinical synovitis and tenosynovitis by ultrasonography (US) 7 score in patients with rheumatoid arthritis treated with synthetic drugs, in clinical remission by DAS28. *Reumatol Clin.* 2017.
19. Hammer HB, Kvien TK, Terslev L. Ultrasound of the hand is sufficient to detect subclinical inflammation in rheumatoid arthritis remission: a post hoc longitudinal study. *Arthritis Res Ther.* 2017; 19(1):221.
20. Perrotta FM, De Socio A, Scriffignano S, Lubrano E. Residual disease activity in rheumatoid arthritis patients treated with subcutaneous biologic drugs that achieved remission or low disease activity: a longitudinal observational study. *Clin Rheumatol.* 2018; 37(6):1449-55.
21. Karimzadeh H, Karami M, Bazgir N, Karimifar M, Yadegarfar G, Mohammadzadeh Z. Ultrasonographic findings of rheumatoid arthritis patients who are in clinical remission. *J Res Med Sci.* 2018; 23:38.
22. Naredo E, Valor L, De la Torre I, Martinez-Barrio J, Hinojosa M, Aramburu F et al. Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? *Arthritis Care Res* (Hoboken). 2013; 65(4):512-7.
23. Janta I, Valor L, De la Torre I, Martinez-Estupinan L, Nieto JC, Ovalles-Bonilla JG et al. Ultrasound-detected activity in rheumatoid arthritis on methotrexate therapy: Which joints and tendons should be assessed to predict unstable remission? *Rheumatol Int.* 2016; 36(3):387-96.
24. Alarcon GS, Lopez-Ben R, Moreland LW. High-resolution ultrasound for the study of target joints in rheumatoid arthritis. *Arthritis Rheum.* 2002; 46(7):1969-70; author reply 70-1.
25. Kaneko Y, Kondo H, Takeuchi T. American College of Rheumatology/European League Against Rheumatism remission criteria for rheumatoid arthritis maintain reliable performance when evaluated in 44 joints. *J Rheumatol.* 2013; 40(8):1254-8.
26. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis.* 2011; 70(1):172-5.
27. Spinella A, Sandri G, Carpenito G, Belletti L, Mascia MT. The discrepancy between clinical and ultrasonographic remission in rheumatoid arthritis is not related to therapy or autoantibody status. *Rheumatol Int.* 2012;32(12):3917-21.
28. van der Leeden M, Steultjens MP, van Schaardenburg D, Dekker J. Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. *Arthritis Res Ther.* 2010; 12(1):R3.
29. van Tuyl LH, Britsemmer K, Wells GA, Smolen JS, Zhang B, Funovits J et al. Remission in early rheumatoid arthritis defined by 28 joint counts: limited consequences of residual disease activity in the forefeet on outcome. *Ann Rheum Dis.* 2012; 71(1):33-7.
30. Wechalekar MD, Lester S, Proudman SM, Cleland LG, Whittle SL, Rischmueller M et al. Active foot synovitis in patients with rheumatoid arthritis: applying clinical criteria for disease activity and remission may result in underestimation of foot joint involvement. *Arthritis Rheum.* 2012; 64(5):1316-22.
31. Wechalekar MD, Lester S, Hill CL, Lee A, Rischmueller M, Smith MD et al. Active Foot Synovitis in Patients With Rheumatoid Arthritis: Unstable Remission Status, Radiographic Progression, and Worse Functional Outcomes in Patients With Foot Synovitis in Apparent Remission. *Arthritis Care Res* (Hoboken). 2016; 68(11):1616-23.
32. Cruces M, Al Snih S, Serra-Bonett N, Rivas JC. Subclinical Synovitis Measured by Ultrasound in Rheumatoid Arthritis Patients With Clinical Remission Induced by Synthetic and Biological Modifying Disease Drugs. *Reumatol Clin.* 2017.
33. Sapundzhieva T, Karalilova R, Batalov A. Musculoskeletal ultrasound for predicting remission in patients with rheumatoid arthritis: results from a 1-year prospective study. *Rheumatol Int.* 2018; 38(10):1891-9.
34. Sapundzhieva T, Karalilova R, Batalov A. Musculoskeletal ultrasound as a biomarker of remission – results from a one-year prospective study in patients with rheumatoid arthritis. *Med Ultrason.* 2018; 20(4):453-60.
35. Raffeiner B, Grisan E, Botsios C, Stramare R, Rizzo G, Bernardi L et al. Grade and location of power Doppler are predictive of damage progression in rheumatoid arthritis patients in clinical remission by anti-tumour necrosis factor alpha. *Rheumatology* (Oxford). 2017; 56(8):1320-5.
36. de Miguel E, Pecondon-Espanol A, Castano-Sanchez M, Corrales A, Gutierrez-Polo R, Rodriguez-Gomez M et al. A reduced 12-joint ultrasound examination predicts lack of X-ray progression better than clinical remission criteria in patients with rheumatoid arthritis. *Rheumatol Int.* 2017; 37(8):1347-56.
37. Filippou G, Sakellariou G, Scire CA, Carrara G, Rumi F, Bellis E et al. The predictive role of ultrasound-detected tenosynovitis and joint synovitis for flare in patients with rheumatoid arthritis in stable remission. Results of an Italian multicentre study of the Italian Society for Rheumatology Group for Ultrasound: the STARTER study. *Ann Rheum Dis.* 2018; 77(9):1283-9.
38. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. *Rheumatology* (Oxford). 2014; 53(11):2110-8.
39. Han J, Geng Y, Deng X, Zhang Z. Subclinical Synovitis Assessed by Ultrasound Predicts Flare and Progressive Bone Erosion in Rheumatoid Arthritis Patients with Clinical Remission: A Systematic Review and Metaanalysis. *J Rheumatol.* 2016; 43(11):2010-8.
40. Lisbona MP, Pamies A, Ares J, Almirall M, Navallas M, Solano A et al. Association of bone edema with the progression of bone

erosions quantified by hand magnetic resonance imaging in patients with rheumatoid arthritis in remission. *J Rheumatol.* 2014; 41(8):1623-9.
41. Gandjbakhch F, Haavardsholm EA, Conaghan PG, Ejbjerg B, Foltz V, Brown AK et al. Determining a magnetic resonance imaging inflammatory activity acceptable state without subsequent radiographic progression in rheumatoid arthritis: results from a followup MRI study of 254 patients in clinical remission or low disease activity. *J Rheumatol.* 2014; 41(2):398-406.
42. Ranganath VK, Motamedi K, Haavardsholm EA, Maranian P, Elashoff D, McQueen F et al. Comprehensive appraisal of magnetic resonance imaging findings in sustained rheumatoid arthritis remission: a substudy. *Arthritis Care Res* (Hoboken). 2015; 67(7):929-39.
43. Lisbona MP, Solano A, Ares J, Almirall M, Salman-Monte TC, Maymo J. ACR/EULAR Definitions of Remission Are Associated with Lower Residual Inflammatory Activity Compared with DAS28 Remission on Hand MRI in Rheumatoid Arthritis. *J Rheumatol.* 2016; 43(9):1631-6.
44. Forslind K, Svensson B. MRI evidence of persistent joint inflammation and progressive joint damage despite clinical remission during treatment of early rheumatoid arthritis. *Scand J Rheumatol.* 2016; 45(2):99-102.
45. Sewerin P, Vordenbaeumen S, Hoyer A, Brinks R, Buchbender C, Miese F et al. Silent progression in patients with rheumatoid arthritis: is DAS28 remission an insufficient goal in RA? Results from the German Remission-plus cohort. *BMC Musculoskelet Disord.* 2017; 18(1):163.
46. Oleszowsky M, Willinek W, Marinova M, Seidel MF. Synovial inflammation analyzed by 3-T magnetic resonance imaging in etanercept-treated patients with rheumatoid arthritis indicates persistent disease activity despite of clinical remission: A pilot study. *Mod Rheumatol.* 2018:1-6.
47. Anandarajah A, Thiele R, Giampoli E, Monu J, Seo GS, Feng C et al. Patients with rheumatoid arthritis in clinical remission manifest persistent joint inflammation on histology and imaging studies. *J Rheumatol.* 2014; 41(11):2153-60.
48. Ramirez J, Celis R, Usategui A, Ruiz-Esquide V, Fare R, Cuervo A et al. Immunopathologic characterization of ultrasound-defined synovitis in rheumatoid arthritis patients in clinical remission. *Arthritis Res Ther.* 2016;18:74.
49. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka S, Norimoto A et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. *Arthritis Care Res* (Hoboken). 2014; 66(10):1576-81.
50. Ciubotariu E, Gabay C, Finckh A, Physicians of the Swiss Clinical Quality Management Program for Rheumatoid A. Joint damage progression in patients with rheumatoid arthritis in clinical remission: do biologics perform better than synthetic antirheumatic drugs? *J Rheumatol.* 2014;41(8):1576-82.
51. Aydin SZ, Gunal EK, Ozata M, Keskin H, Ozturk AB, Emery P et al. Six-joint ultrasound in rheumatoid arthritis: a feasible approach for implementing ultrasound in remission. *Clin Exp Rheumatol.* 2017; 35(5):853-6.
52. Vergara F, Ruta S, Rosa J, Marin J, Garcia-Monaco R, Soriano ER. The value of power Doppler ultrasound in patients with rheumatoid arthritis in clinical remission: Reclassifying disease activity? *Reumatol Clin.* 2018; 14(4):202-6.
53. Picchianti Diamanti A, Navarini L, Messina F, Markovic M, Arcarese L, Basta F et al. Ultrasound detection of subclinical synovitis in rheumatoid arthritis patients in clinical remission: a new reduced-joint assessment in 3 target joints. *Clin Exp Rheumatol.* 2018; 36(6):984-9.
54. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010; 69(9):1580-8.
55. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2014; 73(1):3-5.
56. Prevoo ML, van ,t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 1995; 38(1):44-8.
57. Orr CK, Najm A, Young F, McGarry T, Biniecka M, Fearon U et al. The Utility and Limitations of CRP, ESR and DAS28-CRP in Appraising Disease Activity in Rheumatoid Arthritis. *Front Med* (Lausanne). 2018; 5:185.
58. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* (Oxford). 2003;42(2):244-57.
59. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA et al. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis.* 2001; 60(7):641-9.
60. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol.* 2005; 32(12):2485-7.
61. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum.* 2003; 48(4):955-62.
62. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T,Ostergaard M. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. *Arthritis Rheum.* 2001;44(9):2018-23.
63. Terslev L, Naredo E, Aegerter P, Wakefield RJ, Backhaus M, Balint P et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open.* 2017; 3(1):e000427.
64. Naredo E, D'Agostino MA, Wakefield RJ, Moller I, Balint PV, Filippucci E et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis.* 2013; 72(8):1328-34.
65. Son KM, Song SH, Lim SK, Seo YI, Kim HA. Characteristics of patients with rheumatoid arthritis in clinical remission: the many aspects of DAS28 remission. *Clin Exp Rheumatol.* 2012; 30(6):947-50.
66. Kapral T, Dernoschnig F, Machold KP, Stamm T, Schoels M, Smolen JS et al. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? *Arthritis Res Ther.* 2007; 9(4):R72.
67. Scott IC, Ibrahim F, Panayi G, Cope AP, Garrood T, Vincent A et al. The frequency of remission and low disease activity in patients with rheumatoid arthritis, and their ability to identify people with low disability and normal quality of life. *Semin Arthritis Rheum.* 2018.
68. do Prado AD, Staub HL, Bisi MC, da Silveira IG, Mendonca JA, Polido-Pereira J et al. Ultrasound and its clinical use in rheumatoid arthritis: where do we stand? *Adv Rheumatol.* 2018; 58(1):19.
69. Heegaard C, Dreyer L, Egsmose C, Madsen OR. Test-retest reliability of the disease activity score 28 CRP (DAS28-CRP), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) in rheumatoid arthritis when based on patient self-assessment of tender and swollen joints. *Clin Rheumatol.* 2013; 32(10):1493-500.
70. Neogi T, Felson DT. Composite versus individual measures of disease activity in rheumatoid arthritis. *J Rheumatol.* 2008; 35(2):185-7.