Ultrasound detection of subclinical synovitis in rheumatoid arthritis patients in clinical remission: a new reduced-joint assessment in 3 target joints

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Abstract

Objective

The ability of ultrasound (US) to identify subclinical joint inflammation in rheumatoid arthritis (RA) patients in remission has been already reported. Nonetheless, current studies present a lack of homogeneity in patient's characteristics and number of joints assessed by US. The aim of this study was to identify a reduced set of target joints to be scanned in RA patients in clinical remission in order to detect subclinical synovitis.

Methods

Forty RA patients in clinical remission (DAS28 ≤2.6) for at least 3 months underwent an US examination of 18 joints: wrist, II-III-IV-V metacarpophalangeal (MCP) and II-III-IV-V metatarsophalangeal joints bilaterally. The presence of synovial hypertrophy (SH) and power-Doppler (PD) signal was registered following the OMERACT definitions and was graded according to a 4-point scale (0–3). Then, by applying a process of data reduction based on the frequency of joint involvement, a reduced assessment was obtained.

Results

Twenty (50%) subjects had at least one joint affected by active synovitis; 17.5% presented grade 1 PD and 32.5% grade 2 PD. The joints most frequently affected by active synovitis were the wrists (75%) and the II MCP joints (55%). After data reduction, the evaluation of 3 joints (both wrists and the II MCP of the dominant hand) obtained a sensitivity of 90% for the detection of subclinical synovitis.

Conclusion

The US scan of 3 target joints showed a high sensitivity in detecting subclinical active synovitis in RA patients in clinical remission and can be feasible in the routine assessment of these patients.

Key words
rheumatoid arthritis, remission, ultrasound, power Doppler, active synovitis

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Received on November 13, 2017; accepted in revised form on February 26, 2018.

Competing interests: none declared.

Introduction

In the last decade ultrasound (US) has become an essential tool in the early diagnosis and therapeutic management of rheumatoid arthritis (RA) patients.

In RA patients solid data have demonstrated that US is more sensitive in the detection of joint effusion, synovial hypertrophy (SH) and early structural damage (*i.e.* bone erosions) respectively than clinical assessment and conventional radiography (1-7). The application of PD can allow the detection of pathologic synovial and tenosynovial vascularisation which is associated with active inflammation. Furthermore, previous results have shown the predictive value of PD in relation to structural damage progression and disease flare, making PD a useful tool for monitoring joint disease activity and pathology (1, 8-20). In contrast with these data, two recent RCTs do not support the usefulness of US in monitoring RA patients. In these studies in fact the systematic use of US in patients with early RA was not associated with significant better clinical outcome than a conventional driven strategy (21, 22).

By now, remission represents the main target in the management of RA patients, however it is known that the lack of symptoms does not always mean a lack of joint inflammation and several authors have reported a dissociation between clinical and imaging remission detected by US and MRI (1, 11-20, 23-28). For this reason, the last EULAR recommendations suggest the application of US to assess persistent inflammation in RA patients even when clinical remission is present (1). Nonetheless, current studies are characterised by a lack of homogeneity in patient's characteristics and number of joints assessed by US. There is no consensus yet about which target joints should be included in the US assessment of RA patients in clinical remission, and consequently several sets of joints have been evaluated ranging from a global evaluation of 44 joints to a reduced set of 6 joints (20, 23-30).

As conceivable, to be applicable in a real life scenario in RA patients, the assessment of target joints should be at the same time representative of global disease activity and feasible.

The aim of this study was to identify, in a sensitive and feasible manner, a set of target joints to be evaluated by US in RA patients in clinical remission, in order to detect potential signs of subclinical synovitis.

Patients and methods

Data from 40 consecutive patients with RA according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria (31) and older than 18 years were analysed. Patients data were selected from individuals, attending either the Immunology and Rheumatology Unit of the Department of Clinical and Molecular Sciences S. Andrea University Hospital or the ImmunoRheumatology Unit, Policlinico Universitario Campus Biomedico of Rome, who were in clinical remission (DAS28 ≤2.6) for at least 3 months.

Informed consent was obtained from all patients and the study was performed according to the Declaration of Helsinky.

In each centre an US examination was performed the same day of the clinical assessment, as part of the routine care, by a rheumatologist experienced in musculoskeletal US, who was blinded to the clinical data. A General Electric *Logiq E*9 machine (GE Healthcare, Chalfont St Giles, Buckinghamshire, UK), equipped with a multi-frequency 6-15 MHz linear transducer, was used.

In the absence of a universally accepted set of target joints to be included in the US assessment of RA patients in clinical remission, we focused on the joints that had been most commonly evaluated by previous studies (26, 30). Therefore the US assessment and scanning technique included the evaluation of 18 joints: radiocarpal, II-III-IV-V metacarpophalangeal (MCP) and II-III-IV-V metatarsophalangeal (MTP) joints bilaterally. All joints were examined in longitudinal and transverse scans according to a multiplanar scanning technique, following internationally approved guidelines (32, 33).

The presence of SH and intra-articular PD signal was registered following the Outcome Measures in Rheumatology (OMERACT) definitions, using both GS and PD modalities (33) and was

scored according to a semiquantitative scale (0=absent, 1=mild, 2=moderate, 3=severe).

The settings for PD were the following: frequency 8.3–10 MHz, pulse repetition frequency 600 Hz, gain adjusted just below the level that caused the appearance of noise artifacts, low wall filter. The settings of the two equipment were identical. Inter-observer reliability test (κ coefficient >0.7) between the two US investigators was performed during a pre-study meeting. Images of the joints of patients with RA, with active and inactive disease randomly chosen, were simultaneously scored by each evaluator for SH and PD signal using semiquantitative scales (0–3).

Target joints

For the identification of the target joints, we focused on PD active synovitis rather than tenosynovitis and erosions. Active synovitis is in fact the reference lesion in most of the studies aimed to analyse residual activity in RA patients and it has shown predictive value in relation to radiographic damage progression and clinical relapse (26, 27, 30).

The process of data reduction was based on the frequency of joint involvement within the total 18 joints; a reduced US assessment was selected from different joint combinations, as similarly reported by other authors (34, 35). In brief, we initially considered the joint most commonly presenting active synovitis. Then, positive patients were excluded, and among the remaining subjects, the most frequently affected joint was identified. This procedure was repeated until a combination of joints reached ≥90% sensitivity.

The prevalence of SH positivity and PD positivity was reported according to joint location as number and percentage. We compared the diagnostic performances of different set of assessed joints to detect the presence of PD positivity, using the McNemar test. For each analysis *p*-values <0.05 were considered statistically significant.

Results

The clinical, demographic and laboratory data of the 40 patients are reported in Table I.

Table I. Demographic, clinical and laboratory data of the 40 patients included in the study.

Patients	Sex	Age	DAS28	Disease Duration (years)	Remission (months)	Therapy	ACPA	RF
01	F	48	2	10	12	–	pos	pos
02	F	68	2	12	12	MTX	pos	pos
03	F	76	2	16	12	CCS	pos	pos
04	F	76	1.9	5	12	MTX	pos	pos
05	F	68	2.2	7	12	MTX	pos	pos
06	M	62	2	3	3	MTX + SSZ	pos	pos
07	F	53	2	8	6	MTX	pos	pos
08	F	85	2	15	12	MTX	pos	pos
09	F	70	2.1	15	12	MTX	pos	neg
10	F	57	2	0.5	3	MTX	pos	neg
11	F	55	2.2	1.5	3	SSZ	pos	neg
12	F	70	2.6	10	8	SSZ	pos	pos
13	F	47	2.2	3	6	MTX	neg	neg
14	F	40	2.6	1	4	HCQ	neg	neg
15	F	75	2.6	20	9	MTX	pos	pos
16	F	47	1.3	6	3	MTX	neg	pos
17	F	27	1.2	1	9	HCQ	neg	pos
18	F	54	2.6	14	12	MTX	neg	neg
19	F	68	2.4	20	4	MTX	pos	pos
20	F	26	2.4	1.5	3	HCQ	pos	pos
21	F	58	2.1	8.5	8	–	pos	pos
22	M	53	2.5	11	30	LEF	pos	pos
23	F	54	1.7	7	12	HCQ	pos	pos
24	M	75	2.5	9	25	HCQ	neg	neg
25	F	70	2.6	3	36	HCQ	neg	neg
26	F	74	2.6	9	12	HCQ	neg	neg
27	F	74	2.5	10	15	CCS	neg	neg
28	F	32	2.2	16	12	MTX	neg	neg
29	F	24	2.3	12	12	HCQ	neg	neg
30	M	74	2.2	9	30	HCQ	pos	pos
31	M	45	2.6	9	48	MTX	pos	neg
32	F	64	2.4	3	12	MTX	pos	neg
33	F	58	0.8	1.5	14	–	pos	neg
34	F	55	0.5	2	3	MTX	neg	neg
35	F	29	2.4	5	36	SSZ	neg	neg
36	M	48	2.5	6	36	MTX	pos	pos
37	F	82	2.3	24	24	–	pos	pos
38	F	55	2	12	12	SSZ	pos	pos
39	M	54	2.1	2	3	MTX	pos	neg
40	F	56	2.2	3	6	–	neg	pos
Mean	–	56.7	2.1	8.1	19.9	–	–	–
SD	–	15.9	0.6	5.6	12.9	–	–	–

Mtx: methotrexate; Lef: leflunomide; SSZ: salazopyrin; HCQ: hydroxycloroquine; CCS: corticosteroids; RF: rheumatoid factor; ACPA: anti citrullinated protein antibodies.

Thirty out of 40 (75%) subjects presented SH at least in one joint.

Considering the most severe grade of SH in each patient, 12/40 (30%) had grade 1 and 18/40 (45%) grade 2.

Twenty out of 40 (50%) of the subjects had at least one joint affected by active synovitis (SH plus PD positivity).

Considering the most severe grade of PD signal in each patient, 7/40 (17.5%) presented grade 1 PD and 13/40 (32.5%) grade 2 PD (Figs. 1-2).

Active synovitis and target joints

The joints most frequently affected by active synovitis were the wrists (15/20 patients; 75%) and the II MCP joints (11/20 patients; 55%). The synovial inflammatory activity of the other joints was less frequent: III MCP 20% (4/20 patients), IV MCP 15% (3/20 patients), V MCP 10% (2/20 patients), II-III-IV and V MTP 5% (each of them 1/20 patients) joint (Table II). The dominant side was usually more frequently affected, however the US exam of the contralateral side showed synovial inflammatory activity in additional 7/20 patients (3 at the wrist and at the II MCP, one at the IV MCP).

In the reduced joint count assessment, the evaluation of both wrists and of the

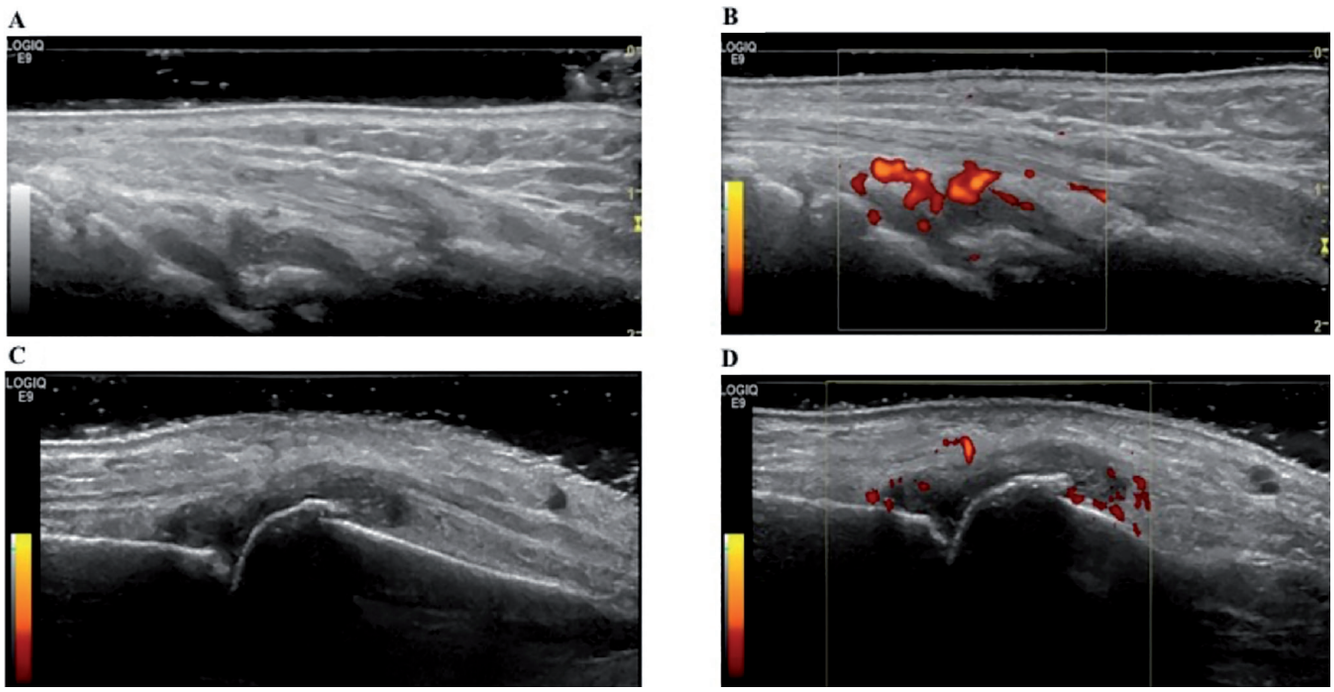

Fig. 1. Moderate synovial hypertrophy of the wrist (**A**); the application of PD shows grade 2 active synovitis (**B**). Moderate synovial hypertrophy of the II MCP joint (**C**); the application of PD shows grade I active synovitis (**D**).

Table II. Presence and grade of synovial hypertrophy (SH) and power Doppler (PD) at every joint site assessed in the study in the dominant and not dominant side.

		DOMINANT									NOT DOMINANT								
		MCP (n/%)				MTP (n/%)				WRIST	MCP (n/%)				MTP (n/%)				WRIST
		II	III	IV	V	II	III	IV	V	(n/%)	II	III	IV	V	II	III	IV	V	(n/%)
SH positive (30)	Grade 1	5 17%	2 7%	2 7%	2 7%	5 17%	5 17%	7 23%	1 3%	12 40%	7 23%	1 3%	1 3%	0 0%	5 17%	2 7%	4 13%	1 3%	14 47%
	Grade 2	5 17%	2 7%	0 0%	0 0%	2 7%	0 0%	0 0%	0 0%	5 17%	3 10%	1 3%	1 3%	0 0%	3 10%	0 0%	1 3%	0 0%	4 13%
PD positive (20)	Grade 1	4 20%	4 20%	2 10%	2 10%	1 5%	1 5%	1 5%	1 5%	6 30%	7 35%	0 0%	0 0%	0 0%	0 0%	0 0%	1 5%	1 5%	9 45%
	Grade 2	4 20%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	5 25%	3 15%	0 0%	1 5%	0 0%	1 5%	0 0%	0 0%	0 0%	3 15%

MCP: metacarpophalangeal; MTP: metatarsophalangeal.

II MCP of the dominant hand allowed to reach a sensitivity of 90% (18/20 patients) by using the lowest number of joints; by adding the contralateral II MCP joint the sensitivity increases up to 100% (Table III).

Discussion

Remission and low disease activity are the therapeutic target in RA patients. However, it has been demonstrated that the lack of clinical signs and symptoms of activity does not always reflect a lack of joint inflammation and the consequent interruption of structural damage progression. Different authors have found active synovitis in RA patients in clinical remission by using high sensitivity techniques such as US or MRI (1, 11-20, 23-28). Furthermore, the presence of residual PD activity appears to be related to the development of clinical flares and structural damage progression (1, 8-20) and its suppression is suggested by the Targeted Ultrasound Initiative Group to achieve complete remission (36).

In our series of RA patients in clinical remission, the evaluation of a core set of 3 joints (both wrists and II MCP of the dominant hand) was highly sensible in detecting subclinical active synovitis and time saving.

The main limit of this study is represented by the small sample size. In addition the cross sectional design can allow to assess the presence of subclinical synovitis but it does not give information on the predictive value of active residual synovitis in relation to RA clinical outcome and structural progression.

By scanning a reduced number of articular sites, we obtained data which are in accordance with previous studies (26, 30). The set of joints previously scanned, was variable, ranging from 6 to 44, with the wrist and the MCP joints of the dominant hand included in all cases (26, 30). Signs of subclini-

Table III. Sensitivity of different sets of target joints in the assessment of active synovitis. *p*-values have been considered for the presence of active synovitis *versus* the 18 joints.

SET OF TARGET JOINTS (Patients with at least one joint affected by active synovitis)			PD signal		*p*-value
			Total Positive	Grade 2	
18 JOINTS	II-V MCP + wrists + II-V MTP bilaterally	n° pts Sensitivity	20 100%	13 100%	NS
1 JOINT	Not dominant wrist	n° pts Sensitivity	12 60%	4 31%	0.01
2 JOINTS	Wrist bilaterally	n° pts Sensitivity	15 75%	8 62%	NS
3 JOINTS	Wrist bilaterally + II dominant MCP	n° pts Sensitivity	18 90%	11 85%	NS
4 JOINTS	Wrist + II MCP bilaterally	n° pts Sensitivity	20 100%	12 92%	NS
DOMINANT SIDE	II MCP + Wrist	n° pts Sensitivity	15 75%	8 62%	NS
	II-V MCP + Wrist	n° pts Sensitivity	15 75%	8 62%	NS
	II-V MCP + Wrist + II-V MTP	n° pts Sensitivity	16 80%	8 62%	NS
NOT DOMINANT SIDE	II MCP + Wrist	n° pts Sensitivity	16 80%	7 54%	NS
	II-V MCP + Wrist	n° pts Sensitivity	16 80%	7 54%	NS
	II-V MCP + Wrist + II-V MTP	n° pts Sensitivity	16 80%	7 54%	NS

MCP: metacarpophalangeal; MTP: metatarsophalangeal.

cal synovitis in PD mode were present from 9 to 62% of cases (26, 30). Lack of correlations was found between the number of joints and the number of patients presenting US subclinical synovitis, thus the evaluation of a reduced number of joints might be considered as a potential strategy (26).

In particular, among the studies that included a reduced number of joints, Brown *et al*. found 43% of active synovitis in 107 RA patients by evaluating the II-V MCP and wrist of the dominant hand (37). Ozgocmen *et al*. reported 61% of PDUS-positive synovitis in 31 RA patients by analysing 12 joints (I-V MCP and wrists bilaterally) (24). Saleem demonstrated 50% of active synovitis by scanning 6 joints (II-V MCP and wrist of the dominant hand) of 128 RA patients (16).

More recently, in response to the last EULAR recommendations for the use of imaging in RA, which have encouraged further studies aimed on the identification of target joints to be scanned in these patients (1), different studies have proposed further reduced sets of target joints to make the assessment of subclinical synovitis feasible in the daily clinical practice. Particularly, Elkhouly *et al*. reported a 70% of PD positivity ≥1 and 29% ≥2 by analysing a set of 22 joints in 41 RA patients in clinical remission (38). Other authors showed that a US 12-joints scanning (wrist, II-V MCP, ankle, and II-V MTP bilaterally) is highly sensitive for detecting residual B-mode and PD synovitis as compared with a global US assessment in RA patients in clinical remission and have a predictive value in detecting unstable remission (27, 28). De Miguel *et al*., by using the same 12 joints set, concluded that US may predict a lack of x-ray progression in RA better than composite indices of disease activity (39). Rosa *et al*. reported that the evaluation of 6 joints (wrist, II and III MCP bilaterally) present similar good correlation with indices of disease activity as compared to more comprehensive sets of 10 (wrists, II-III MCP and II-III proximal interphalangeal bilaterally) and 22 joints (wrists plus all bilateral MCP and proximal interphalangeal plus bilateral interphalangeal of the thumb), and proposed it as a quick evaluation of active disease versus remission (29). Aydin *et al*. confirmed those data by showing that the US screening of the same 6-joints had a sensitivity of 75% in the detection of subclinical PD grade ≥2 with respect to a set of 38 joints (40).

When compared to previous reports, the present study presents the advantage of having demonstrated that the assessment of a very limited number of joints (bilateral wrists and II MCP of the dominant hand) has a very high sensitivity in the identification of active synovitis. Furthermore, by adding the contralateral II MCP, the sensitivity increased up to 100%.

In conclusion, in our series of RA patients in clinical remission, the US evaluation of 3 target joints allowed to reach a high sensitivity in detecting subclinical active synovitis. If confirmed in larger cohort population, this reduced evaluation of target joints could be useful in the routine assessment of patients in remission, in order to detect in a feasible manner potential sites of subclinical synovitis.

Key messages

- Nowadays there is no consensus about which target joints should be included in the US assessment of RA patients in clinical remission.
- In our series the evaluation of a core set of 3 joints: both wrists and II MCP of the dominant hand, was highly sensible in detecting subclinical active synovitis and time saving.

References

1. COLEBATCH AM, EDWARDS CJ, OSTERGAARD M *et al*.: Eular recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 804-14.
2. HMAMOUCHI I, BAHIRI R, SRIFI N *et al*.: A comparison of ultrasound and clinical examination in the detection of flexor tenosynovitis in early arthritis. *BMC Musculoskelet Disord* 2011; 12: 91.
3. KEEN H, WAKEFIELD R, CONAGHAN PG: Optimising ultrasonography in rheumatology. *Clin Exp Rheumatol* 2014; 32: S13-6.
4. NAREDO E, BONILLA G, GAMERO F *et al*.: Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis* 2005; 64: 375-81.
5. DOUGADOS M, JOUSSE-JOULIN S, MISTRETTA F *et al*.: Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 828-33.
6. MANDL P, KURUCZ R, NIEDERMAYER D *et al*.: Contributions of ultrasound beyond clinical data in assessing inflammatory disease activity in rheumatoid arthritis: current insights and future prospects. *Rheumatology* (Oxford) 2014; 53: 2136-42.
7. NAREDO E, IAGNOCCO A: One year in review: ultrasound in arthritis. *Clin Exp Rheumatol* 2016; 34: 1-10.
8. TERSLEV L, VON DER RECKE P, TORP-PEDERSEN S *et al*.: Diagnostic sensitivity and specificity of Doppler ultrasound in rheumatoid arthritis. *J Rheumatol* 2008; 35: 49-53.
9. FILIPPUCCI E, IAGNOCCO A, SALAFFI F *et al*.: Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. *Ann Rheum Dis* 2006; 65: 1433-37.
10. NAREDO E, MOLLER I, CRUZ A *et al*.: Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2248-56.
11. KAWASHIRI SY, SUZUKI T, NAKASHIMA Y *et al*.: Ultrasonographic examination of rheumatoid arthritis patients who are free of physical synovitis: power Doppler subclinical synovitis is associated with bone erosion. *Rheumatology* (Oxford) 2014; 53: 562-69.
12. MOLENAAR ET, VOSKUYL AE, DINANT HJ *et al*.: Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004; 50: 36-42.
13. BROWN AK, CONAGHAN PG, KARIM Z *et al*.: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2958-67.
14. FOLTZ V, GANDJBAKHCH F, ETCHEPARE F *et al*.: Power Doppler but not low-field MRI predict relapse and radiographic disease progression in rheumatoid arthritis patients with low disease activity. *Arthritis Rheum* 2012, 64: 67-76.
15. PELUSO G, MICHELUTTI A, BOSELLO S *et al*.: Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 172-75.
16. SALEEM B, BROWN AK, QUINN M *et al*.: Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. *Ann Rheum Dis* 2012; 71: 1316-21.
17. DOHN UM, EJBJERG B, BOONEN A *et al*.: No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis* 2011; 70: 252-58.
18. SCIRÈ CA, MONTECUCCO C, CODULLO V *et al*.: Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatology* (Oxford) 2009; 48: 1092-97.
19. WAKEFIELD RJ, D'AGOSTINO MA, NAREDO E *et al*.: After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? *Ann Rheum Dis* 2012; 71: 799-03.
20. GENG Y, HAN J, DENG X, ZHANG Z: Deep clinical remission: an optimised target in the management of rheumatoid arthritis? Experience from an ultrasonography study. *Clin Exp Rheumatol* 2016; 34: 581-6.
21. HAAVARDSHOLM EA, AGA AB, OLSEN IC *et al*.: Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. *BMJ* 2016; 354: i4205.
22. DALE J, STIRLING A, ZHANG R *et al*.: Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis* 2016; 75: 1043-50.
23. WAKEFIELD RJ, FREESTON JE, HENSOR EM *et al*.: Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 1564-67.
24. OZGOCMEN S, OZDEMIR H, KIRIS A *et al*.: Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. *South Med J* 2008; 101: 240-45.
25. SALEEM B, BROWN AK, KEEN H *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: 792-98.
26. TEN CATE DF, LUIME JJ, SWEN N *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: R4
27. NAREDO E, VALOR L, DE LA TORRE I *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: 512-17.
28. JANTA I, VALOR L, DE LA TORRE I *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: 387-96.
29. ROSA J, RUTA S, SAUCEDO C *et al*.: Does a Simplified 6-Joint Ultrasound Index correlate well enough with the 28-joint disease activity score to be used in clinical practice? *J Clin Rheumatol* 2016; 22: 179-83.
30. BEN ABDELGHANI K, MILADI S, SOUABNI L *et al*.: Role of ultrasound in assessing remission in rheumatoid arthritis. *Diagn Intervent Imaging* 2015; 96: 3-10.
31. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-88.
32. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist II. Ultrasonography of the hand and wrist. *Clin Exp Rheumatol* 2006; 24: 118-22.
33. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-87.
34. PERRICONE C, CECCARELLI F, MODESTI M *et al*.: The 6-joint ultrasonographic assessment: a valid, sensitive-to-change and feasible method for evaluating joint inflammation in RA. *Rheumatology* (Oxford) 2012; 51: 866-73.
35. FICJAN A, HUSIC R, GRETLER J *et al*.: Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). *Arthritis Res Ther* (Hoboken) 2014; 16: 476.
36. AYDIN SZ, PAY S, INANC N *et al*.: Targeted Ultrasound Initiative (TUI) Steering Committee. Which joints and why do rheumatologists scan in rheumatoid arthritis by ultrasonography? A real life experience. *Clin Exp Rheumatol* 2017; 35: 508-11.
37. BROWN AK, QUINN MA, KARIM Z *et al*.: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying anti rheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761-73.
38. ELKHOULY T, ELNADY BM, MOHAMED HAMED RAGEH M: Validity of Doppler subclinical synovitis as an activity marker associated with bone erosions in rheumatoid arthritis patients during clinical remission. *The Egyptian Journal of Radiology and Nuclear Medicine* 2016; 47: 985-90.
39. DE MIGUEL E, PECONDÓN-ESPAÑOL A, CASTAÑO-SÁNCHEZ 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: 1347-56.
40. AYDIN SZ, GUNAL EK, OZATA M *et al*.: Six-joint ultrasound in rheumatoid arthritis: a feasible approach for implementing ultrasound in remission. *Clin Exp Rheumatol* 2017; 35: 853-56.