The Egyptian Journal of Radiology and Nuclear Medicine (2016) 47, 985–990

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

www.elsevier.com/locate/ejrnm
www.sciencedirect.com

ORIGINAL ARTICLE

Validity of Doppler subclinical synovitis as an activity marker associated with bone erosions in rheumatoid arthritis patients during clinical remission

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Received 21 February 2016; accepted 23 May 2016
Available online 21 June 2016

KEYWORDS

Rheumatoid arthritis (RA);
Musculoskeletal ultrasonography (MSUS);
Gray scale (GS);
Color Doppler (CD);
Disease modifying anti-rheumatic drugs (DMARDs)

Abstract *Introduction:* Clinical remission is a realistic goal in rheumatoid arthritis (RA) patients. Doppler signals-synovitis may also be considered predictive of clinical flare-ups in RA. Objective: The aim of this study was to detect subclinical synovitis and erosions by musculoskeletal ultrasound (MSUS) in RA patients with clinical remission and free from physical synovitis.

Materials and methods: 41 RA patients were studied who achieved clinical remission for at least 6 months proved by clinical disease activity index (CDAI) and DAS28 without tender neither swollen joints. MSUS of 22 joint done for each patient, the data of gray scale (GSUS) and color Doppler ultrasound (CDUS) graded on a semi-quantitative scale from 0 to 3.

Results: The percentage of RA patients with subclinical synovitis present in at least one joint with CDUS $\geqslant 1$, and CDUS $\geqslant 2$ were 70.7% and 29.2% respectively. The results of CDUS were significantly lower with biologic agents compared to patients on conventional disease modifying anti-rheumatic drugs (DMARDs) alone ($p = 0.01$). There was a strong association between CDUS synovitis and MSUS bone erosions ($p < 0.00001$).

Conclusion: Doppler detected subclinical synovitis could be considered a reliable marker to appraise disease activity in RA patients compared to DAS28 and CDAI, in associated joint destruction secondary to erosions.

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Peer review under responsibility of The Egyptian Society of Radiology and Nuclear Medicine.

1. Introduction

Rheumatoid arthritis (RA) treatment has improved dramatically over the past decades with the early and intensive use

http://dx.doi.org/10.1016/j.ejrnm.2016.05.017

of disease modifying anti-rheumatic drug (DMARDs) strategies (1) and the introduction of biological agents (2). If inflammation is not treated effectively earlier structural damage in RA will occur. Targeted treatment reduces inflammation; therefore, the start of an early, tailored treatment with conventional and/or biological (DMARDs), corticosteroids, coupled with a 'treat to target' (T2T) strategy aiming remission, represents the ultimate goal (3). Disease activity assessment in RA is important for treatment efficiency and predicting the disease outcome. Thus, a sensitive imaging method coupled with thorough clinical examination is required to monitor the disease progress. Clinical remission is considered a realistic therapeutic goal in RA patients (4).

New classification criteria (5) and new remission criteria (6) have been published. It is suggested that imaging techniques such as ultrasonography (US) could be used for additional joints assessment as noninvasive technique without radiation exposure (5).

In particular, gray-scale ultrasonography to detect synovitis and Doppler signals at multiple joint levels could be modified after effective therapy (7). Doppler signals serve as a useful adjunct to gray-scale imaging; thus, it is more sensitive for the detection of early disease and furthermore, it could be more accurate to differentiate between chronic and acute disease of the thickened synovium (8).

Residual Doppler signals-synovitis is also predictive of clinical flare-ups in RA (9). RA patients with clinical remission who have residual Doppler signals synovitis do not achieve true remission theoretically; they are at risk for subsequent structural damage and flare. However, the subjects in the above studies had slightly tender or swollen joints upon physical examination in spite of the fact that they achieved clinical remission (9–14).

The aim of this study was to detect subclinical synovitis and erosions by gray scale ultrasound (GSUS) and Color Doppler ultrasound (CDUS) in RA patients with clinical remission and free from physical synovitis.

2. Materials and methods

2.1. Patients

Forty-one patients who had been diagnosed as RA according to the 2010 ACR/EULAR criteria (15) were consecutively recruited from Al Hada Armed Forces Hospital, Rheumatology Clinic. We included in this study all of the patients achieved clinical remission [disease activity score (DAS28 $\leqslant$ 2.6) and clinical disease activity index (CDAI $\leqslant$ 2.8)] for at least 6 months at the time of MSUS examination. Furthermore, all the patients did not have any tender or swollen joints among 28 sites at the time of MSUS examination (see Figs. 1–3).

Exclusion criteria included any patient who did not fulfill the ACR/EULAR criteria, any patient with DAS28 > 2.6 or CDAI > 2.8 score within the previous 6 months of MSUS examination, and any patients with tender or swollen joints among 28 sites at the time of MSUS examination.

Patients gave their informed consent and The Commission Hospital Ethics and Research Committee approved the study.

2.2. Clinical and laboratory assessment

Clinical evaluation was performed by two Rheumatologists who were blinded to the MSUS findings. Disease activity was evaluated by the DAS28-ESR and CDAI (16). The rheumatoid factor (RF), the anti-cyclic citrullinated peptide antibodies [(anti-CCP Abs) done by the chemiluminescence microparticle immunoassay (CMIA)], ESR (by Westergren method), C-reactive protein ((CRP) using the enzyme linked immunosorbent assay (ELISA)] technique and clinical disease activity were evaluated on the day of the MSUS examination.

2.3. MSUS assessment

Each patient underwent MSUS assessment evaluation by an expert radiologist who was blinded to the clinical findings. A systematic multiplanar GSUS and CDUS examination of 22 joints was performed with the same scanner (Philips CX50) using a multifrequency linear transducer (5–12 MHz) and Philips L15-7Io Compact Linear Array (Hockey Stick) 23MM Transducer (15–7 MHz). The US score included the following 22 joints: bilateral wrists and finger joints including the first to fifth MCP joints, the first IP joint and the second to fifth PIP joints. All joint regions were examined in a standardized manner according to the EULAR and JCR guidelines (17).

Gray scale (GSUS) synovitis was diagnosed by presence of joint effusion (JE) and/or synovial hypertrophy (SH). The presence of JE/SH was identified in each joint as abnormal anechoic/isoechoic intra-articular material according to the Outcome Measures in RA Clinical Trials (OMERACT) definitions (18). Each joint was scored for both GSUS and CDUS on a semiquantitative scale from 0 to 3 (19). Synovial hypertrophy in GSUS is as follows:

Grade 0 = absence which means no synovial thickening.
Grade 1 = mild, which means minimal synovial thickening obliterating the angle between the periarticular bones without bulging over the line linking the tops of the bones.
Grade 2 = moderate, which means synovial thickening bulging over the line linking the tops of the periarticular bones but without extension to at least one bone diaphysis.
Grade 3 = marked, synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to at least one of the bone diaphysis.

Considering that minimal effusion can be detectable even in healthy subjects, in particular, the maximum distance from the bony surface and the capsule was 2 mm for MCP, PIP, wrists, and 4 mm for knee according to Naredo et al. (20) Doppler signal was graded on a semi-quantitative scale from 0 to 3:

0 = absence or minimal flow.
1 = mild: single vessel signal.
2 = moderate: confluent vessels.
3 = marked: vessel signals in >50% of the joint area.

Doppler frequency was set higher for the study of small joints and superficial tissues, and lower for deep structures. Color gain was set just below the level that causes the appearance of noise artifacts. In the latest generation US systems, the difference between CDUS and PDUS is not so evident because

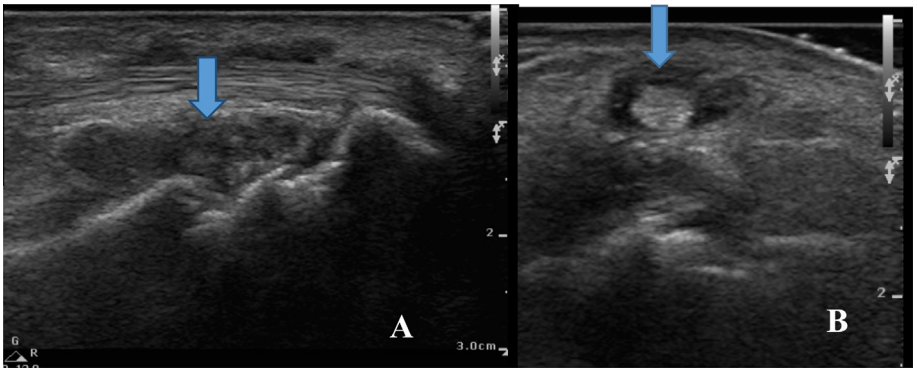

Fig. 1 GSUS longitudinal (A) and transverse (B) scan of the wrist in RA patient shows hypoechoic fluid encasing the extensor tendon denoting tenosynovitis with synovial hypertrophy (arrow) and effusion of the wrist joint.

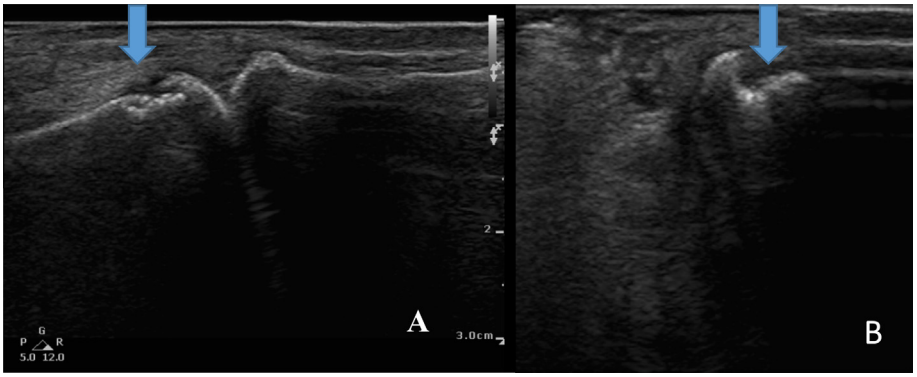

Fig. 2 GSUS longitudinal (A) and transverse (B) scan of the MCP joint in RA patient shows irregular cortical outline and discontinuity denoting erosions (arrows) not detected in plain radiograph.

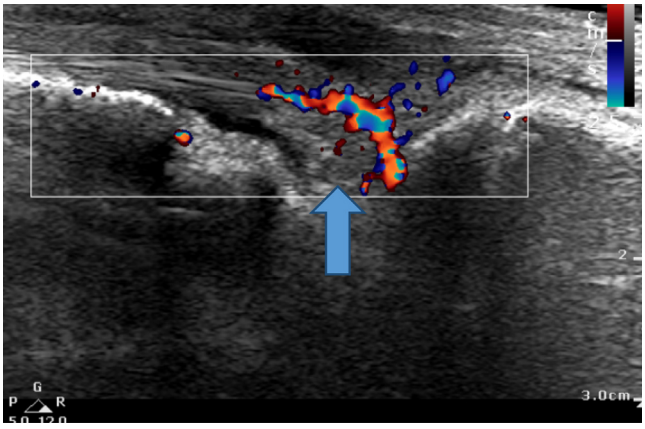

Fig. 3 CDUS longitudinal scan of the wrist joint in RA patient shows hypo and isoechoic soft tissue signal of synovial hypertrophy (arrow) with mild effusion and color Doppler signal grade 2 suggestive of acute/active synovitis.

CDUS has gained insensitivity and PDUS provides information also on the flow direction (20).

The presence of tenosynovitis was defined as abnormal hypoechoic or anechoic appearance of the tendon with or without fluid inside the tendon sheath with positive Color Doppler signals in two perpendicular planes (21). An erosion is defined by a cortical break seen in two perpendicular planes (19).

2.4. Statistical analysis

Data were collected, tabulated, and analyzed using the scientific package of social statistics version 22. The mean, standard deviation and statistical significance were calculated by Student's "*t*" test for paired data. The Mann–Whitney test using the standard error of the mean to calculate *z* was used for comparison of CDUS and GSUS parameters and its relation to medications. Fisher's test and the Chi square test were used to compare the probability of variables. A value of $p < 0.05$ was considered statistically significant. Correlation coefficient "*r*" for the relationship of different variables was calculated using Pearson's coefficient for quantitative data and Spearman's correlation for qualitative non-parametric data.

3. Results

Forty-one RA patients achieved definite clinical remission, with a mean age, disease duration, duration of remission, ESR, CRP: 50.4 ± 13.8 years, 9.5 ± 7.6 years, 9.6 ± 6.7 months, 25.8 ± 5.3 mm/1st hour and 1.8 ± 0.74 mg/L respectively. Twenty patients (48.7%) were treated with conventional cDMARDs (12 patients with MTX/HCQ

combination, 5 patients with SSZ/HCQ/MTX combination and 3 patients on leflunomide/HCQ combination). Also there were twenty -one patients (51.3%) on combination of cDMARDs and biologic DMARDs (bDMARDs) (7 patients on abatacept, 7 patients on etanercept, 5 patients on adalimumab, one patient on rituximab and one patient on tocilizumab). All the patients achieved Boolean remission. In addition, none of the patients exhibited tender or swollen joints on their established medications.

The number (%) of RA patients achieved clinical remission, with subclinical synovitis present in at least one joint in GSUS $\geqslant$ 1, and GSUS $\geqslant$ 2 was 75.6% and 31.7% respectively [GS grade 1, was 18 (43.9%); GS grade 2, was 10 (24.4%); GS grade 3, was 3 (7.3%)]. However CDUS $\geqslant$ 1, and CDUS $\geqslant$ 2 were 70.7% and 29.2% respectively [CD grade 1, was 17 (41.5%); CD grade 2, was 9 (21.9%) and CD grade 3, was 2 (7.3%)].

The clinical characteristics were compared between patients with subclinical CDUS synovitis and patients without CDUS synovitis, and between patients with CDUS grade $\geqslant$2 (0/1) and patients with CDUS grade $\geqslant$2 (2/3) (Table 1). There were no statistical significance differences between the studied groups regarding age, sex disease duration, duration of remission, RF, CCP Abs, and CRP, while statistically significant differences were found regarding tenosynovitis ($p = 0.02$) and GSUS ($p = 0.03$) in CDUS +ve and −ve subgroups. Also, statistically significant differences regarding ESR ($p = 0.004$), bony erosions ($p = 0.001$) and GS ($p = 0.004$) were found to be lower in patients with CDUS 0/1 rather than patients with CDUS 2/3.

The use of cDMARDs and disease activity was not different among the groups (Table 2). However, the results of CDUS were significantly lower regarding the use of biologic agents compared to patients on cDMARDs only ($p = 0.01$).

We confirmed an association between CDUS synovitis with MSUS bone erosions during scanning in 902 joints from 41 patients. As shown in Table 3, there was a strong association between CDUS synovitis and MSUS bone erosion ($p < 0.00001$).

4. Discussion

Many clinically inactive RA patients have evidence of persistent synovitis on magnetic resonance imaging (MRI) or musculoskeletal ultrasound (MSUS) scanning (22). Joint inflammation determined by MSUS or MRI not by physical examination is defined as subclinical synovitis (9,10). The Doppler US subclinical synovitis, has been proven by several studies showing that its presence is considered predictive for radiographic progression in the future (9,23).

In our study, none of the RA patients had tender or swollen joints upon physical examination and achieved clinical remissions with subclinical synovitis present in at least one joint in GSUS $\geqslant$ 1, and GSUS $\geqslant$ 2 were 75.6% and 31.7% respectively, while in CDUS $\geqslant$ 1, and CDUS $\geqslant$ 2 were 70.7% and 29.2% respectively.

Wakefield et al. study published regarding this issue in the Annals 2004, highlighted the relative insensitivity of routine clinical examination in identifying inflamed joints, and suggested that subclinical synovitis may be common (24). This hypothesis further analyzed in Harman et al. study 2015 and showed that persistence of the PDUS signal led to radiographic deterioration (25).

The positivity rate of anti-CCP Antibodies was 29% in Scire et al. (9), and RF 41% in Sakellariou et al. (26); however, the present cases were 68% regarding RF and 53% regarding anti-CCP Antibodies which were much higher than the previous ones, thus may have influenced our results. In addition, regarding therapies, the absence of CDUS synovitis was likely to be associated with bDMARDs which support the evidence of biologic agents is superior to cDMARDs in terms of radiologic progression (27).

So patients who do not exhibit active disease can be considered for alternative therapeutic approaches that are more likely to be beneficial. The idea of routine MSUS examination into the assessment of RA disease activity will require careful

Table 2 Comparisons between treatment regimens regarding GSUS and CDUS ultrasound findings.

Treatment	Number	z	P value
GSUS cDMARDs bDMARDs total	20 21 41	−2.895	0.07
CDUS cDMARDs bDMARDs total	20 21 41	−2.757	0.01

Table 1 Clinical and demographic characters of the studied patients.

	CDUS −VE (16)	CDUS +VE (25)	P-value	CDUS 0/1 (27)	CDUS 2/3 (14)	P-value
Age, mean/SD	49.7 ± 13.8	50.6 ± 14.07	0.877	49.1 ± 13.8	55 ± 13.5	0.331
Sex, female/male	13/3	18/7	0.65	20/7	11/3	0.4
Disease duration (months), mean/SD	13.25 ± 8.89	8.56 ± 5.7	0.09	9.3 ± 6.3	11.42 ± 8.8	0.535
Duration of remission (years), mean/SD	14.5 ± 8.91	10.84 ± 11.82	0.423	12.7 ± 5.2	9.42 ± 3.7	0.486
+ve CCP (n), %	6 (37.5%)	17 (68%)	0.48	15 (55.5%)	8 (57.1%)	0.38
+ve RF (n), %	12 (75%)	17 (68%)	0.55	19 (70.4%)	10 (71.4%)	0.3
CRP mean/SD, mg/L	1.6 ± 0.7	2 ± 0.77	0.43	1.8 ± 0.8	2.3 ± 0.74	0.49
ESR mean/SD, mm/1st hour	19 ± 8.2	14.88 ± 7.4	0.241	13.8 ± 6.2	19.6 ± 11.7	0.004
DAS 28, mean/SD	1.5 ± 0.3	1.75 ± 0.56	0.189	1.67 ± 0.57	1.62 ± 0.3	0.8
CDAI median (range)	0.7 (0–2)	0.6 (0–2)	0.5	0.6 (0–2)	0.1 (0–2)	0.25
Tenosynovitis (n), %	1 (6.3%)	6 (24%)	0.02	2 (7.4%)	5 (35.7%)	0.4
Erosions (n), %	1 (6.3%)	14 (56%)	0.057	4 (14.8%)	11 (78.6%)	0.001
GSUS (n), %	8 (50%)	23 (92%)	0.034	18 (64%)	13 (92.8%)	0.004

Table 3 Comparison between the presence of CDUS signals and its association with bony erosions.

	CDUS −VE	CDUS +VE	*P*-value	Sensitivity	Specificity	−VE LR	+VE LR
Bone erosion −VE	806	81	< 0.00001**	95%	99.88%	118.92	0.85
Bone erosion +VE	1	14					

Fisher's test.
** Highly statistical significance.

consideration. However, till now there is no universal agreement upon a limited joint set or MSUS definition of active disease. The joint set used in our study was similar to a number of proposed sets that are currently being implemented in Shin et al. 2014 study (28).

Since the existence of Doppler signals was considered a risk factor for further radiologic progression in RA (23), the suppression of Doppler signals by biologic agents may explain the preferential protective effect. Also, we found that the percentage of patients with US bone erosion was higher in those with subclinical CDUS synovitis than in those without CDUS synovitis. Furthermore, the frequency of the joints with US bone erosions was much higher in the joints with CDUS signals as compared with the joints without CDUS signals. These data support the coexistence of CDUS signals with US bone erosions in RA even after they have achieved definitive clinical remission (28).

It would be reasonable for patients with Doppler synovitis to show a high GSUS score, which was also significant in our study. In RA patients, Doppler signals with GSUS thickening of synovial tissues reflect synovial cell hyperplasia with neovascularization (29).

This supports the hypothesis that clinical assessment alone is inaccurate to guide therapeutic decisions and that radiologic remission may be a more appropriate treat to target parameter for optimizing outcomes (28). However, other studies suggested that radiographic progression in patients with DAS28 remission is restricted to those patients who continue to have clinical evidence of joint inflammation. Patients with sustained DAS28 remission have very little disease progression (30). Lane et al. (25) suggested that the challenge lies not only with the clinical assessment but also with the durability and extent of clinical response. The current study supports the hypothesis of routine MSUS examination within clinical disease assessment in RA facilitates more accurate measurement of disease activity and consequently management decisions. It is well known that tapering biologics or non-biologics DMARDs after clinical remission in RA patients who fulfilled remission criteria is associated with percentage of relapse rates (31). Naredo et al. (2015) results suggested that Doppler-detected synovitis could predict treatment tapering failure in RA patients in sustained clinical remission (32). So delaying tapering of medications in those with subclinical CDUS synovitis could stop possible future relapse and improve the clinical outcome.

As stated by the Targeted Ultrasound Initiative Group (33), to achieve imaging remission the suppression of residual Doppler synovitis is suggested as a target. Thus, our present data may emphasize the importance of subclinical Doppler synovitis and suggest that it may be a promising marker to achieve complete remission in RA patients.

To conclude, Doppler subclinical synovitis persistence in RA patients achieving clinical remission free from physical synovitis is to be considered as reliable activity marker compared to DAS28 and CDAI especially in associated joint destruction due to erosions. However larger-scale longitudinal randomized controlled trials are needed to confirm our findings. Overall, the message from this work is to question quiescence of RA and possible value of treating disease in clinical remission but CDUS positive synovitis. Considerably larger, more powerful studies will be needed to make the case for routine US follow-up of RA and possibility of treatment escalation or tapering for clinically quiescent disease.

Conflict of interest

The authors declare that there are no conflict of interests.

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