Assessment of Disease Activity in Rheumatoid Arthritis: A Comparative Study of Clinical Evaluation with Ultrasonography

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ABSTRACT:

BACKGROUND:

In patients with rheumatoid arthritis (RA) a poor relation on an individual joint basis, has been observed between clinical signs of synovitis and ultrasound measures of synovial disease.

OBJECTIVE:

To compare the traditional clinical measures of disease activity with the ultrasound (US) features of synovitis, and investigate the relationship between composite US measures and disease activity score in 28 joints (DAS28), clinical disease activity index (CDAI), their components and other variables of disease activity in RA.

METHODS:

Fifty patients with RA were enrolled in this study. The following 28 joints including bilateral glenohumeral, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) of the hands, and knee joints were assessed for tenderness and swelling. DAS28 and CDAI were determined for each patient. A systematic US examination was carried out by a radiologist for the 28 clinically examined joints. Each joint was evaluated for the presence of synovial hypertrophy (SH), power Doppler (PD) signals, and effusion. The following composite US measures of synovial disease were made: SH joint count (SHJC), effusion joint count (EJC), PD joint count (PDJC), SH index (SHI), and PD index (PDI).

RESULTS:

Joints with tenderness only showed significantly less PD scores than other groups. SH and PD signals were detected in 32.1% and 27.8% of the Nil group respectively. SHJC and SHI showed moderate correlation with TJC and high correlation with SJC, evaluator global assessment (EGA), patient global assessment (PGA), DAS28, CDAI, and erythrocyte sedimentation rate (ESR). PDJC and PDI showed moderate correlations with tender joint count (TJC), and high correlation with swollen joint count (SJC), EGA, DAS28, and ESR. PDI showed high correlation with PGA, and CDAI.

CONCLUSION:

Traditional clinical signs used in the evaluation for disease activity may bear different relation to the US features of synovitis (SH, PD signals). Composite US count and indices for SH and PD relate significantly to the DAS28-ESR, CDAI, and their components.

KEY WORDS: rheumatoid arthritis, synovitis.

INTRODUCTION:

In patients with rheumatoid arthritis (RA), accurate assessment of joint inflammation and regular monitoring of disease activity is essential in evaluating response to treatment and disease outcome [(1)]. Synovitis plays an important role in the joint-destroying process in RA[(2)]. In this case, the monitoring of response to therapy in patients with RA should focus on synovitis. In clinical practice, examination of the joints for the presence of tenderness and soft tissue swelling is traditionally implicated to determine whether active inflammation is present. However, the relative importance of these two clinical signs is unclear [(3)].

In addition, clinical scoring methods for the assessment of arthritis currently used in clinical trials and daily practice are of insufficient sensitivity and reproducibility[(4)], and subjected to

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both intra- and inter-observer variability, particularly in the evaluation of joint tenderness[5].

Ultrasound (US) is more sensitive than clinical examination in the detection of synovitis[6,7]. It has been shown to detect subclinical synovitis, which can predict radiographic progression in both the early and established stages of disease[8]. Several studies clearly demonstrated the significance of both grey-scale (GS) and Doppler US for detecting and evaluating inflammatory activity in synovial joints[9-11]. Both color Doppler ultrasound (CDUS) and power Doppler ultrasound (PDUS) techniques detect synovial flow, which is a sign of increased synovial vascularization. The presence of intra-articular power Doppler (PD) signal aids in distinguishing active synovitis from inactive intra-articular thickening [12].

Discrepancies between clinical and US measures in individual joints may be overcome by composite counts or scores from several joints, which taken together may be more representative of total disease activity in the patient[13].

As synovitis appears to be the best predictive marker of future damage in an individual RA joint , the aim of this study is to compare the traditional clinical measures of disease activity, joint swelling and tenderness, with the US features of synovial disease, using PD data , and investigates the relationship between composite US measures and disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR), clinical disease activity index (CDAI), their components and other variables of disease activity(pain, fatigue) in adult RA.

MATERIALS AND METHODS:

This cross sectional study was conducted on 50 patients fulfilling the 1987 ARA criteria for RA[14], who were recruited from the rheumatology unit in Baghdad Teaching Hospital, Medical City, Baghdad, Iraq from February 2014 to December 2014. The patients were receiving regular treatment with a disease modifying antirheumatic drug and/or biological agents (etanercept, Infliximab, or rituximab), with or without low dose steroid in the three months before the investigation. Patients who have traumatic, septic, or microcrystalline arthritis, marked joint deformity, and previous joint surgery, were excluded. Written informed consent was obtained from all patients prior to study inclusion.

Clinical evaluation: The following data were recorded for each patient at study entry: age, sex, occupation, duration of symptoms, drugs received for RA at entry, body weight, body mass index, and rheumatoid factor.

The following 28 joints including bilateral glenohumeral, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) of the hands, and knee joints were evaluated for clinical evidence of disease activity (the presence or absence of tenderness and/or swelling) according to the standard criteria[15]. These joints were then categorized into 4 groups (I) both swollen and tender (S+T), (II) swollen only (S-only), (III) tender only (T-only) or (IV) neither swollen nor tender (Nil).

In addition, tender joint count (TJC28), swollen joint count (SJC28), patient global assessment (PGA; 0-10 VAS) and evaluator global assessment (EGA; 0-10 VAS) of disease activity were recorded, and DAS28 and CDAI were determined for each patient. The following clinical variables were also recorded: pain score (0-10 VAS), fatigue (0-10 VAS), and blood was taken for ESR analysis by standard laboratory technique.

Ultrasound evaluation: At the same appointment for clinical assessment, the patients underwent an US examination by a specialist radiologist who was blinded to all clinical information. A systematic ultrasound examination of the 28 joints clinically investigated was carried out by using a high resolution real time US unit (Philips HD 11, USA), employing 7.5-12 MHz linear array transducer. A combination of GSUS and PD imaging were used throughout the examination.

This scanning method has been conducted in a standardized modified manner according to EULAR guidelines[17]. The MCP and PIP joints were first examined using dorsal and volar approaches through both transverse and longitudinal scanning. The wrists were examined using dorsal longitudinal scanning (radial, median, ulnar).

In glenohumeral joint the Posterior recess is examined with the transducer transversal to the humerus, and the shoulder in neutral position, and axillary recess is examined with the transducer longitudinal to the axilla, and the shoulder in 90° of abduction. Elbow joint is scanned longitudinally and transversally, from the anterior recess with the joint in extension. In the knee joint suprapatellar (longitudinal and transverse), medial and lateral longitudinal scanning are performed in supine neutral position.

Each one of the 28 joints was evaluated for the presence of synovial hypertrophy (SH), effusion, and PD signals. Joint ultrasound findings were defined according to published Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions[17]. For each examined joint, SH and PD were graded using a four-grade semiquantitative scoring system from 0 to 3[18,19]. The highest SH and PDUS grade detected during the scans was adopted as representative of each joint, respectively.

From this the following composite US measures of synovial disease were made:

(i) Joint count for US SH (SHJC): the number of joints scoring either 1,
2 or 3, out of a total of 28 (0-28).

(ii) Joint count for US effusion (EJC): the number of joints with effusion out of a total of 28(0-28).

(iii) Joint count for PD signal (PDJC): the number of joints scoring either 1,
2 or 3, out of a total of 28 (0-28).

(iv) 28 joint index for SH (SHI): the sum of the SH scores obtained from each of the 28 joints (0-84).

(v) 28 joint index for PD (PDI): the sum of the PD scores obtained from each of the 28 joints.

US synovitis referred to a joint that demonstrate the presence of 1 or more of the US abnormalities (SH, effusion, or PD signal)[20].

Statistical analysis

Data of the studied group were entered and analyzed by using the statistical package for social sciences (SPSS) software for windows, version 20. Correlations between clinical and US parameters were calculated using Spearman's test. Correlations were considered to be high, moderate, or poor when they were >0.7, 0.4–0.7, or <0.4, respectively.

RESULTS:

Patient characteristics: Fifty patients with RA were enrolled in this cross sectional study. The mean age of patients was 45±8.2 years (range 28-61), 80% of patients were female. The mean disease duration was 8.4±6.5 years (range1-25). Rheumatoid factor was positive in 54%. Values of clinical, laboratory, and US measures of disease activity are shown in table 1.

Table 1:The range, mean and S.D. of clinical, laboratory and US measures of Disease activity in 50 patients with RA.

Disease activity parameter	Range	Mean	S.D.
TJC28	0-27	10.4	8.6
SJC28	0-23	8.8	6.9
PGA	1-10	5.7	3
EGA	0-9	4.8	3
VAS pain	0-10	5.48	2.94
VAS fatigue	0-10	5.30	2.72
ESR	3-135	41.2	32.6
DAS28-ESR	1.5-7.6	5.2	1.9
CDAI	2-67	29.6	19.7
SHJC	7-25	15.6	5.3
PDJC	5-22	13	4.7
EJC	0-14	5.5	3.3
SHI	8-42	21.46	9.4
PDI	5-36	18	8

SHJC, synovial hypertrophy joint count; PDJC, power Doppler joint count; EJC, effusion joint count; SHI, synovial hypertrophy index; PDI, power Doppler index

In total, 1,400 joints were assessed both clinically (table2) and with US.

Clinical findings: On clinical examination, 677 joints (48.36%) had clinical evidence of disease activity; while 723(51.64%) joints were normal on clinical examination.

US findings: On US evaluation, 772 joints (55.14%) had synovial hypertrophy, 273 joints (19.5%) had joint effusion, and 652 joints (46.57%) had PD signal. A total of 827 joints (59.1 %) had US synovitis (i.e., had 1 or more of the 3 US abnormalities).

Table 2: Distribution of clinically examined joints per clinical groups.

Clinical Groups	The joint						
	PIP	MCP	Wrist	Elbow	Shoulder	Knee	Total
Nil	303(60.6%)	228(45.6%)	36(36%)	48(48%)	58(58%)	50(50%)	723(51.6%)
T-only	93(18.6%)	42(8.4%)	18(18%)	30(30%)	34(34%)	18(18%)	235(16.8%)
S-only	24(4.8%)	118(23.6%)	10(10%)	0	0	4(4%)	156(11.1%)
T+S	80(16%)	112(22.4%)	36(36%)	22(22%)	8(8%)	28(28%)	286(20.4%)
Total	500	500	100	100	100	100	1400

S+T, both swollen and tender; S-only, swollen only; T-only, tender only; Nil, neither swollen nor tender; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

Comparison of US scores between clinical groups: Median scores (and ranges) for each of US SH and PD per clinical group are shown in Table 3. The Kruskal–Wallis test was used to compare the differences between multiple groups. This demonstrated significant differences between the four clinical groups for the US SH score and the PD score.

The **Mann–Whitney U-test** was used to assess differences between the clinical groups pair wise, for the significant Kruskal–Wallis outcome variables. Regarding the **US SH scores**, Mann-Whitney U-test revealed no significant difference between the S-only and T+S groups (P=0.056), while all the other between- group comparison were statistically significant. Concerning the **US PD scores**, Mann-Whitney u-test reveals no significant difference between the nil and tender groups (P=0.539), while all the other between-group comparison were statistically significant (P=0.0001).

The SH and PD scores and their grading per clinical groups are shown in figure 1 and 2 respectively.

Table 3: Median and range of US scores per clinical groups.

US variables	Nil	T-only	S-only	T+S	K-W P-value
PD score(0-3)	0.0(0-3)	0.0 (0-3)	1.0(0-3)	1.0(0-3)	0.0001
SH score(0-3)	0.0(0-2)	0.0 (0-2)	1.0(0-3)	2.0(0-3)	0.0001

S+T, both swollen and tender; S-only, swollen only; T-only, tender only; Nil, neither swollen nor tender; K-W P-value, Kruskal–Wallis P-value

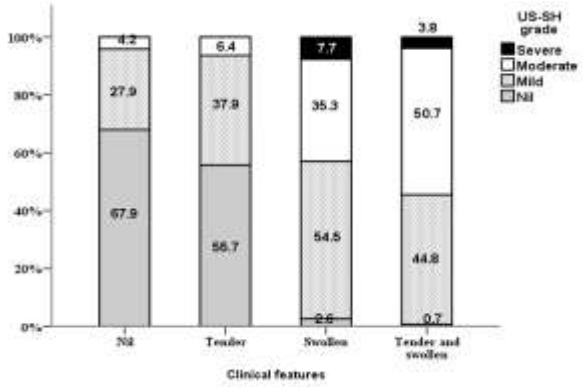

Figure 1: Percentage of SH and their grading per clinical groups

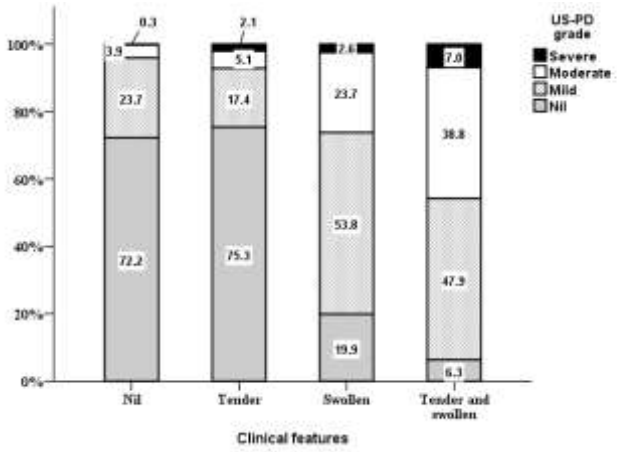

Figure 2: Percentage of PD signals and their grading per clinical groups.

Correlation between clinical and US parameters: Table 8 shows the Spearman's correlations between clinical and US parameters. US joint count and index for SH showed moderate correlation with TJC28 and high correlation with SJC28, VAS pain, VAS fatigue, EGA, PGA, DAS28, CDAI, and ESR. US joint count and index for PD showed moderate correlations with TJC28, and high correlation with SJC28, EGA, DAS28, and ESR. The US joint index for PD shows high correlation with VAS pain, VAS fatigue, PGA, and CDAI, while the US joint count for PD showed moderate correlation. US joint count for effusion show no correlation with TJC28, VAS pain, VAS fatigue, PGA, EGA, CDAI, and ESR, and poor correlation with SJC28, and DAS28.

Table 4: Spearman's correlations between clinical and ultrasonographic features.

	SHI	SHJC	PDI	PDJC	EJC
TJC28	.649**	.609**	.624**	.496**	.239
SJC28	.901**	.874**	.772**	.809**	.287*
VAS pain	.755**	.714**	.713**	.608**	.292
VAS fatigue	.773**	.730**	.730**	.622**	.236
EGA	.818**	.785**	.760**	.785**	.272
PGA	.810**	.765**	.751**	.662**	.271
DAS28	.841**	.814**	.802**	.744**	.282*
CDAI	.821**	.782**	.750**	.680**	.263
ESR	.776**	.744**	.754**	.748**	.197
* significant (p = 0.05); ** highly significant (p=0.01)					

DISCUSSION:

In this study, the results demonstrate highly significant statistical difference between most of the clinical groups regarding the US synovial hypertrophy score and PD score.

Data from the Nil group demonstrate that an apparently normal joint may have synovial hypertrophy and increased vascularity undetectable on clinical assessment. These findings are in accordance with the previously published data from RA patients, using GSUS and PD.[7,8,21,22] Indeed, it has been suggested that synovitis undetected clinically (but detectable by US) may be responsible for continuing erosive damage in patients with clinically controlled RA.[20,23]

Data from the T-only group demonstrate that this clinical sign, on its own, does not appear to be indicative of the underlying synovitis in RA. There was no significant difference in the PD score between the T-only group and the Nil group, with PD signals were being detected in 24.7%. This suggest that tenderness on its own in RA does not appear to be a sign of increased vascularity and, by implication, synovitis. Factors that might explain this observation include the subjective nature and variability in the threshold

for reporting tenderness[24,25]. A variety of alternative non-synovial structures from which tenderness might emanate, including damaged bone and periarticular tissues. Tenosynovitis, concomitant fibromyalgia and/or osteoarthritis influence clinical assessments, resulting in a variable sensitivity and specificity of clinical examination to detect joint inflammation in RA[26,27]. These findings are supported by two other studies in RA[7,28].

Data from the S-only group demonstrate that it is more likely to show US SH and PD signals in comparison with the nil and T- only group , but less in comparison with the T+S groups . This means that soft tissue swelling in a rheumatoid joint usually, but not always, associated with increased synovial vascularity and, by implication, active synovitis. Many previous studies have taken the view that an S-only joint is not inflamed, and classified the joints in this category as inactive[29,30]. Our data suggest that this is inappropriate, and are supported by finding from more recent studies [3,7,31,32]. Joint damage and functional impairment, which are highly important adverse outcomes of RA, have been repeatedly shown to be associated with clinical disease activity, in particular with swollen joint counts [33,34].

Joints that are both swollen and tender appear the most likely to be inflamed, demonstrated by the significantly higher PD scores in the S+T group compared with the T-only, S-only and Nil joints, with PD signals being detected in 93.7% of the joints in this group (35.8% being grade 2 and 3). In keeping with our findings, previous studies have found that US determined synovitis were most frequent in joints which are swollen and tender [3,28].

US variables (count and indices for SH and PD signal) showed significant moderate-high correlation with TJC, SJC, PGA, EGA, VAS (pain, fatigue), DAS28, CDAI, and ESR. This association was stronger for the GS measures than the PD measures, and generally stronger for the joint indices than the joint count, for both GS and PD. GSUS primarily detects hypertrophy of the synovium, which may become chronically thickened and less reversible in established RA[8] .The level of GS synovitis appear to correlate well with disease duration, probably reflecting previous inflammation and subsequent fibrotic changes[35]. In contrast, the presence of PD is independent of disease duration and therefore appear to be a better marker of inflammation at any given time point[36].

Previous studies reported variable results comparing the number of TJ and SJ, PGA, EGA, VAS (pain, fatigue) and sonographic findings[7, 13, 31]. A relevant consideration in this regard is that the strength of association between manual and ultrasound joint counts diminishes as patients are in or near to remission[37]. In cohorts with high disease activities, manual joint counts better correlate with sonography, whereas in the setting of low disease activity or remission, divergent results are observed [7,13,37, 38]. The patients in our cohort had, on average, high level of disease activity; the mean DAS28 was 5.18±1.86, the median was 5.4. Damjanov N. et al. have found significant positive linear correlations between US DAS and DAS-28, patients' and physicians' VAS assessments of activity, and ESR[4]. In his cohort average DAS-28 at baseline was in the range of high disease activity 5.80 ±1.24. In agreement with our results, other studies showed that GSUS and/or PDUS scores were moderately to strongly associated with DAS-28, CDAI, as well as with ESR [7,13,39].

Other factors could be also responsible for the variable results of previous studies comparing US scoring systems and clinical indicators of disease activity. Disease duration could be an influencing factor, based on its well observed correlation with GS synovitis. In addition, the correlation of the scoring systems with clinical indicators of inflammatory activity seems to vary with the size and number of joints evaluated, as well as positions evaluated in the joint[40]. Terslev et al. have found that scoring systems in his study only correlate with the CRP, but not with DAS-28 or any other single component. This is probably because only a single position in a single joint was evaluated[41]. In a study applying three positions in the wrist and in studies with multi-joint assessments, a correlation with DAS-28 has been demonstrated[11,42]. US examination for synovitis is mostly carried out from the dorsal aspect of the finger joint, although Scheel et al showed that synovitis was most often detected in the palmar proximal area (86%) of the affected finger joints[43]. Recently, Vlad et al came to the same conclusion. They showed that palmar US findings correlated more strongly with clinical scores than dorsal US findings[44].

Our study was limited by the lack of assessment on inter- and intraobserver agreement; however, a good reliability of sonography in RA patients was reported previously[11,45].

CONCLUSION:

Traditional clinical signs used in the evaluation for disease activity may bear different relation to the US features of synovitis (SH, PD signals). Joints with both swelling and tenderness are the most likely to show US synovitis, followed by joints that show swelling only. Joints which are only tender are the least likely to show US synovitis. Joints that are normal on clinical examination (neither swollen nor tender) may show US synovitis (subclinical synovitis). Composite US count and indices for SH and PD relate significantly to the DAS28-ESR, CDAI, their component, and VAS for pain and fatigue.

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