Verification of an ultrasonographic scoring system in discriminating rheumatoid arthritis from osteoarthritic and normal joints in an Egyptian cohorts

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Background
The use of musculoskeletal ultrasound in rheumatoid arthritis (RA) has been growing over the last decades mainly to monitor response to treatment and for early detection of erosions. Suggestions to include this technique in the diagnosis of RA have been made, but not yet been implemented (because of the lack of specific sonographic criteria for RA).
Objectives
To verify the performance of a proposed combined structural and synovial scoring system in differentiating RA from osteoarthritis (OA) and healthy sonographic findings in the small joints of the hand.
Patients and methods
Twenty RA patients, 20 patients with hand OA, and 10 healthy controls were subjected to musculoskeletal ultrasound of the metacarpophalyngeal and proximal interphalyngeal joints. The novel proposed scoring system was applied characterizing each joint as either RA supported or RA unsupported. Grading of synovitis as mild, moderate, or severe was also performed. In the RA group, disease activity was assessed by Disease Activity Score 28 (DAS28) and anticyclic citrullinated peptide serum levels were measured.
Results
When one or more RA-supported joints were detected using this scoring system, it had a sensitivity of 100.0% and a specificity of 83.0%, with a diagnostic accuracy of 90.0%, for the diagnosis of RA. If two or more joints were detected, it had a sensitivity of 95.0% and a specificity of 96.7%, with a diagnostic accuracy of 96.0% for the diagnosis of RA.
Conclusion
The novel suggested combined structural and synovial scoring system showed high performance in differentiating RA from OA and controls.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder in which the immune system targets synovial joints and causes mild to severe joint destruction with extra-articular manifestations. It is associated with significant disability and socioeconomic costs because it is estimated to affect up to 1% of the world's adult population [1]. RA is two to three times more prevalent in women than in men; it may begin as early as infancy, but onset usually occurs in the third or the fourth decade [2].

To monitor treatment efficiency and predict disease outcome, it is important to assess disease activity and joint damage in RA [3]. Conventional radiography has long been the standard method of identifying progressive joint damage in arthritis. This method is, however, not sensitive for the detection of soft tissue changes, for example,

synovitis, and usually does not reveal early erosive lesions [4,5].

The use of musculoskeletal ultrasound (US) in rheumatology has increased considerably over the past decade both as a result of technological developments and to facilitate early identification and treatment of inflammation [6].

High-quality US machines with good resolution have provided rheumatologists with a means of identifying inflammation and structural damage, monitoring disease, and predicting therapeutic responses. US has clear advantages over other imaging tools such as MRI in terms of better tolerability, an ability to scan multiple joints in one sitting, and its ability to directly correlate clinical and imaging findings [7].

The Outcome Measures in Rheumatology network (OMERACT) definitions for US pathology provide a

consensus for defining inflammatory changes, but have not been recommended as a clinical tool for use in the diagnosis of inflammatory arthritis [8].

In RA, synovitis appears to be the primary abnormality, and bone damage occurs in proportion to the level of synovitis, but not in its absence [9]. Proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints are usually among the first to be affected in RA, and findings in these joints are considered to be markers of overall joint damage in RA patients [10].

Several quantitative and semiquantitative classification systems for the grayscale US evaluation of joint synovitis and Doppler examination have been studied. These scoring systems have been correlated with synovial pathology and MRI findings, and have been shown to be more sensitive than clinical joint evaluation. They are also important in the prediction of development of RA in undifferentiated synovitis, detection response to RA therapy, and prediction of joint damage [3,11–13].

There is increasing evidence that synovitis with findings similar to RA plays a significant role as a contributor in the disease pathogenesis in osteoarthritis (OA). These scoring systems for RA synovial disease have not used OA joints as controls, but normal controls [14]. Elevated synovial disease scores could be identified using these scoring systems in OA hands [15–17].

In response to the need for a score to distinguish not only normal from pathological but also degenerative from inflammatory joints, Kunkel and colleagues, suggested a clinical scoring system of hand arthritis using a combined structural/qualitative/quantitative approach that incorporates published normal values for synovial cavity volume of the MCP and PIP joints [18], anatomical descriptions of the positions of synovial fluid and synovial proliferation, Doppler signal, and the visible structural detail of osteophytes and erosions, incorporating OA as controls with high specificity and sensitivity for RA [6].

We aimed to verify the performance of a proposed combined structural and synovial scoring system in differentiating RA from OA and healthy sonographic findings in the small joints of the hand.

Patients and methods
Clinical assessment
This study was cross-sectional and was carried out on 20 RA patients diagnosed according to the American College of Rheumatology (ACR) 1987 criteria [19], 20 patients with hand OA diagnosed according to the ACR 1990 criteria [20], and 10 healthy volunteers with no hand complaints or systemic arthritis. They were recruited from the Internal medicine, Physical medicine, Rheumatology, and Rehabilitation inpatient and outpatient clinics at Ain Shams University Hospital. All patients were subjected to a full assessment of medical history, and a thorough clinical examination including a detailed musculoskeletal examination. Disease activity was assessed on the basis of the Disease Activity Score 28 (DAS28 score) [21].

RA patients with a family history of hand OA as well as OA patients with associated hyperuricemia and/or gout were excluded. All participants provided written informed consents to participate after receiving a full explanation of the study, which was approved by our local Ethics Committee.

Laboratory assessment
Laboratory investigations performed included complete blood count by flow cytometry using a coulter counter, erythrocyte sedimentation rate using the Westergren method, rheumatoid factor using an enzyme-linked immunosorbent assay method, and serum anticyclic citrullinated peptide (anti-CCP) using the enzyme-linked immunosorbent assay method.

Radiological assessment
Musculoskeletal ultrasound
US examination of MCP and PIP joints of the right hand was performed using General Electric Logiq P5 R4.0.× with a multifrequency linear transducer 3–11 MHz (General Electric, Milwaukee, Wisconsin, USA). US was performed by a certified sonographer who was blinded to the clinical diagnosis. Doppler imaging was performed using the semiquantitative scoring system for synovitis in RA patients [3] including 10 joints/patient: first to fifth fingers' MCP and PIP joints for the detection and grading of effusion (visualized as a black, anechoic area) and synovial hypertrophy (visualized as hypoechoic or hyperechoic structure within the region affected by effusion): 0 'absent'; 1 'minimal'; 2 'moderate'; or 3 'extensive'.

As pathophysiologically, in the majority of cases, both effusion and thickening in synovial tissue appear concurrently, and for simplification in clinical practice, both synovial hypertrophy and effusion were combined in a measure and referred to as synovitis.

Synovitis was measured, standardized, and scored according to a semiquantitative method and statistical cutoffs were identified using the receiver operating characteristic (ROC) curve analysis. Quantitative cutoffs between different semiquantitative US scores for each joint (MCP or PIP) are shown in Table 1.

Table 1 Semiquantitative US scores

Joints/score	0/1*	1/2	2/3
MCP synovitis (mm)	0.58	1.75	2.08
PIP synovitis (mm)	0.63	1.15	1.83

MCP, metacarpophalyngeal; PIP, proximal interphalyngeal; US, ultrasound; *The cutoff between scores of 0 and 1 is considered to distinguish between 'healthy' and 'pathologic'.

Color Doppler scores were semiquantitative and graded 0 to 3 as follows [12,13]: 0 (normal): absence of power Doppler signal, 1 (mild): a few vessel dots, 2 (moderate): confluent vessel dots over less than or equal to half the area of synovium, and 3 (severe): confluent vessel dots over greater than or equal to half the area of synovium. Also, the resistive index (RI) was measured. RI = peak systolic flow–end diastolic flow/peak systolic flow, where low values of RI denote low resistance, indicating inflammation, and high values denote high resistance, which is normal in resting musculoskeletal tissues. When spectral Doppler measurements could not be measured because of the lack of detectable vascularization in the joint examined, the RI was recorded as 1.00 as the resistance in the synovial arteries was presumed to be the same as extrasynovial musculoskeletal flow [22].

The combined structural/synovial score [6]

This is a novel scoring system that was developed using a combination of synovial and bony structural parameters in an attempt to better differentiate RA patients from OA and normal controls. This system was defined so that each MCP or PIP joint could be evaluated independently and classified as 'RA supported' or 'RA unsupported' depending on the findings. Classifying a joint as 'RA supported' is equivalent to stating that 'the bony, Doppler, and/or synovial findings in this joint are suggestive of RA' (Figs 1–3).

Step 1

The presence or absence of an osteophyte is determined. This leads to automatic classification of the joint as 'RA unsupported'. The next joint may be assessed without further review.

Step 2

When no clear osteophytes are present, the presence or absence of erosions and Doppler signal are established. A joint is defined as having an erosion if a cortical breach greater than 1 mm in width is visible in two orthogonal planes. Any erosion or Doppler signal greater than 1 establishes a joint as 'RA supported'.

Step 3

Finally, the presence or absence of abnormal synovial tissue or fluid is established. Visible synovial tissue/
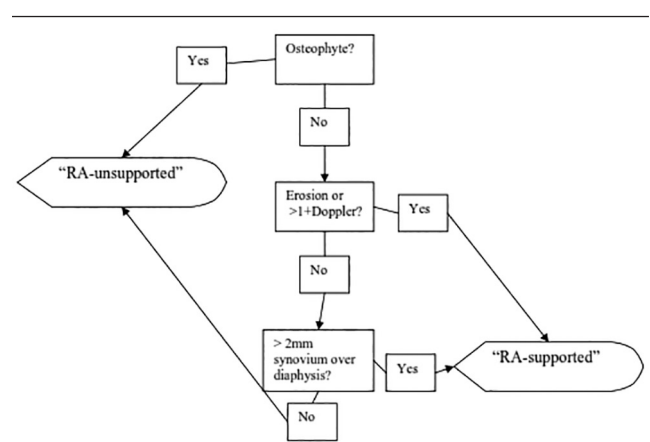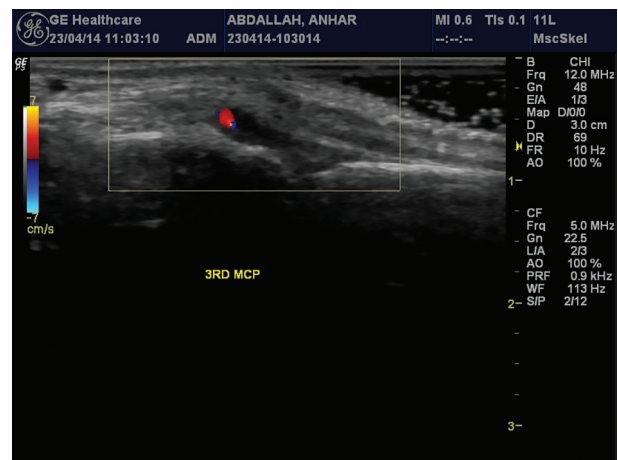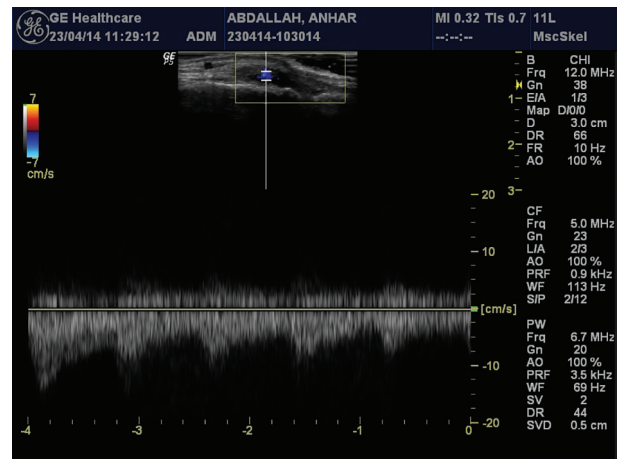
Figure 1

Diagram of combined structural/synovial Score (Kunkel *et al.*, 2012)

Figure 2

Grade 1 semi-quantitative vascularity assessment by Doppler

Figure 3

Measuring RI in joints with positive Doppler signal

fluid is defined as anechoic fluid or hypoechoic tissue, distinguishable from the normal, homogenous dorsal

intracapsular tissue or volar palmar plate in each joint, and seen in any scanning plane. To classify a joint as 'RA supported', this hypoechoic tissue or anechoic fluid must be visible along the proximal or distal diaphysis of either joint-forming bone with a quantitative cutoff of more than 2 mm of visible synovium/fluid as measured perpendicularly anywhere from the diaphyseal surface.

Plain radiography was also performed for the diagnosis and grading of hand OA (grade 0–4) [23].

Statistical analysis

The collected data were analyzed using the statistical package for social sciences program software, version 18.0 (SPSS Inc., Chicago, Ilinois, USA).

Descriptive statistics were calculated for quantitative parametric data as minimum and maximum of the range as well as mean ± SD, and for numerical nonparametric data as median and first and third interquartile range; qualitative data were described as number and percentage.

Inferential analyses were carried out for quantitative variables using Mann–Whitney U-test in cases of two independent groups with nonparametric data and the analysis of variance for more than two independent groups with parametric data.

For qualitative data, inferential analyses for independent variables were carried out using the χ^2-test to determine differences between proportions. Correlations were assessed using the Spearman ρ-test for numerical nonparametric and qualitative data.

The ROC curve was used to evaluate the performance of different tests to differentiate between certain groups.

A P value less than 0.05 was considered to be significant and P values less than 0.01 or less than 0.001 was considered to be highly significant; all other values were considered to be nonsignificant.

Results

This study was carried out on 20 RA patients, 20 patients with hand OA including two erosive OA patients, and 10 healthy individuals who served as a control group. Some demographic data of the patients and the controls are shown in Table 2.

There was no significant difference between the study groups in age and sex. The duration of RA disease ranged from 0.3 to 15 years, with a median interquartile range of 2 (0.5–7.8).

Clinical and laboratory data in the RA group

Among the 20 RA patients, the modified DAS28 score ranged from 3.0 to 8.1, mean ± SD 6.0 ± 1.5. Five patients (25%) had low/moderate disease activity (DAS28 from 3.2–5.1) and 15 (75%) had high disease activity (DAS28>5.1). The laboratory investigations of the RA patients showed positive anti-CCP in all patients, with titer ranging from 32.0 to 320.0 IU/ml, mean ± SD 164.0 ± 77.9. Two patients (10.0%) had low/moderate positive anti-CCP and 18 patients (90.0%) had high positive anti-CCP.

Radiological findings in the OA group

Among the 20 OA patients, two patients (10.0%) had grade 1 (by K-L grading), nine patients (45.0%) had grade 2, seven patients (35%) had grade 3, and two patients (10.0%) had grade 4 and showed radiographic findings of erosive OA.

Quantitative and semiquantitative findings by US in RA patients

Vascularity assessment in RA patients utilizing Doppler US and defining on the basis of the maximum grade in each patient showed that nine patients (45.0%) had grade 0, five patients (25.0%) had grade 1 (Fig. 2), six patients (30.0%) had grade 2, and none (0.0%) had grade 3, with the total number of joints with a positive Doppler signal among the 200 joints examined ranging from 0.0 to 30.0, median interquartile range 10.0 (0.0–20.0). RI ranged from 0.71 to 1.00; the minimum RI measured in joints with positive Doppler signals (Fig. 3) had a mean ± SD of 0.88 ± 0.12.

Table 2 Demographic data of the study groups

Demographics	RA	OA	Control	P
Age (years)				
Mean ± SD	56.8 ± 10.2	58.5 ± 5.2	55.4 ± 10.6	0.516 (ANOVA test)
Range	36.0–70.0	50.0–70.0	42.0–69.0	
Sex				
Male	2 (10.0%)	1 (5.0%)	1 (10.0%)	0.816 (χ^2-test)
Female	18 (90.0%)	19 (95.0%)	9 (90.0%)	

ANOVA, analysis of variance; OA, osteoarthritis; RA, rheumatoid arthritis.

Comparisons between patients with a moderate degree of synovitis (Fig. 4) (12 patients) and those with a severe degree of synovitis (eight patients) in terms of anti-CCP, DAS, and RI are shown in Table 3 and Fig. 5, and indicated a significant difference in RI.

Combined Structural and synovial assessment of all study groups, RA, OA, and healthy controls, in the diagnosis and differentiation of the RA group from the other groups showed the following.

(1) The number of RA-supported joints was significantly higher in the RA groups than the OA and control groups, with no significant difference between the OA and the control groups as shown in Table 4. RA-supported joints showed erosion (Fig. 6) and/or Doppler and/or increased synovial thickness more than 2 mm, whereas RA-unsupported joints showed osteophytes (Fig. 7) and/or synovium less than 2 mm and no Doppler signal.

(2) The results showed that an increase in the number of RA-supported joints (because of the presence of erosion, abnormal synovium more than 2 mm, positive Doppler signal and total) was significant in the diagnosis of RA as shown in Table 5 and the ROC curve in Fig. 8.

Some cutoff points were suggested from the results with high diagnostic characteristics for the number of

Table 3 Comparison between patients according to synovitis grade (by US) and anti-CCP, DAS28, and minimum RI

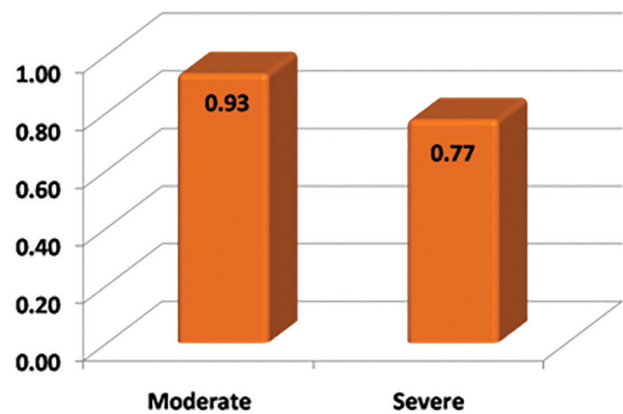| Variant	Moderate	Severe	$P^{\#}$
Anti-CCP (IU/ml)	165.2 ± 80.1	161.7 ± 80.0	0.926
DAS	5.7 ± 1.3	6.7 ± 1.7	0.155
Minimum RI	0.93 ± 0.11	0.77 ± 0.05	0.002*

CCP, cyclic citrullinated peptide; DAS, Disease Activity Score; RI, resistive index; US, ultrasound; #Independent *t*-test; *Significant.
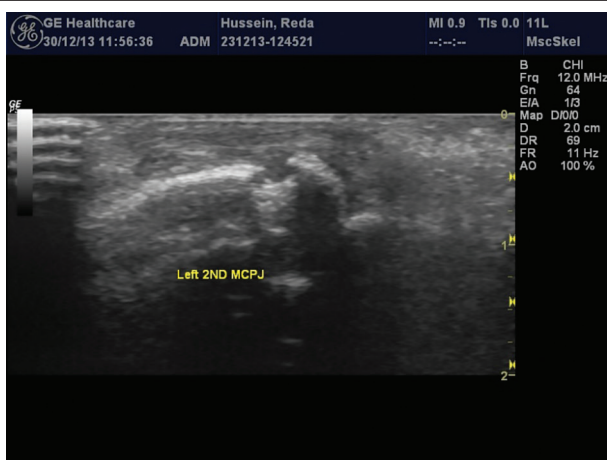
Figure 4
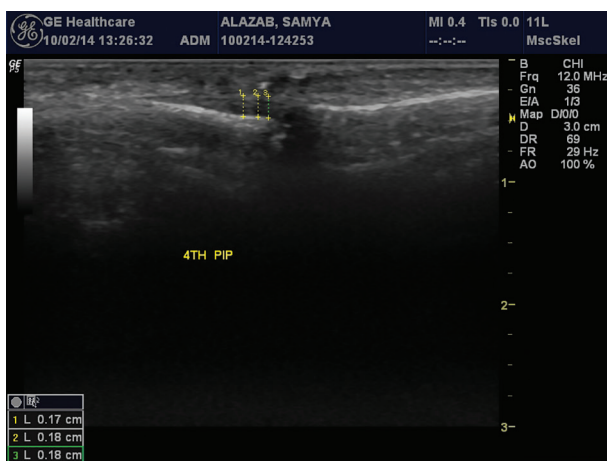
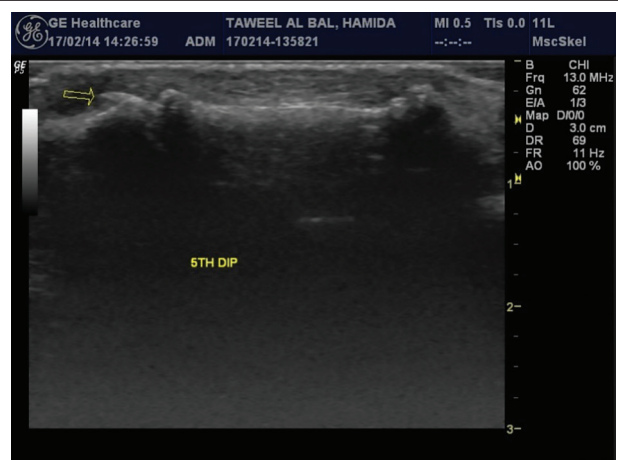Grade 2 moderate synovitis (1.7 mm in 4th PIP joint)

Figure 5

Comparison between maximum synovitis severity (by ultrasound) in terms of minimum resistive index.

Figure 6

An erosion in 2nd MCP joint

Figure 7

An osteophyte in the 5th DIP Joint (arrow)

Table 4 Comparison between study groups in the number of RA-supported joints by US

RA-supported joints	RA	OA	Control	RA/OA (Mann–Whitney test) P	RA/control (Mann–Whitney test) P	OA/control (Mann–Whitney test) P
Erosion						
Median (IQR)	0.0 (0.0–1.8)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.014*	0.014*	0.309
Range	0.0–5.0	0.0–2.0	0.0–0.0			
Doppler						
Median (IQR)	1.0 (0.0–2.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<0.001**	0.005*	1.000
Range	0.0–3.0	0.0–0.0	0.0–0.0			
Synovium>2 mm						
Median (IQR)	3.0 (2.3–4.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<0.001**	<0.001**	1.000
Range	1.0–8.0	0.0–1.0	0.0–1.0			
Total						
Median (IQR)	3.0 (2.3–4.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<0.001**	<0.001**	0.476
Range	1.0–8.0	0.0–2.0	0.0–1.0			

IQR, interquartile range; OA, osteoarthritis; RA, rheumatoid arthritis; US, ultrasound; *Significant; **Highly significant.

RA-supported joints by US in the diagnosis of RA as shown in Table 6.

In the RA group, correlations were assessed between the value of anti-CCP and the number of RA-supported joints; the results showed that there was a positive correlation between anti-CCP and the number of RA-supported joints because of the presence of erosions; this was almost statistically significant, but did not reach significance ($P = 0.064$). Otherwise, there was no significant correlation with other parameters as shown in Table 7 and Fig. 9.

Also in the RA group, correlations were assessed between the value of modified DAS28 and the number of RA-supported joints because of different parameters and the number of joints with synovitis detected by US (by semiquantitative scoring system), which showed a nonsignificant positive correlation (Table 8).

Discussion

Despite the presence of current US scoring systems evaluating degrees of synovitis and inflammation among RA patients, none has been used to diagnose the disease. These have instead been used to assess the presence of inflammatory synovitis and its degree. Hence, they represent a tool for monitoring, but as yet, there is no consensus for the differentiation of RA from other common arthritis such as OA.

In this observational cross-sectional study, using combined structural synovial scoring system developed by Kunkel *et al.* [6] in all three study groups, we found that the number of RA-supported joints (because of the presence of erosion, abnormal synovium more than 2 mm, and one or more Doppler signals in the absence of osteophytes) was significantly higher in the RA group (100.0% of patients had at least one RA-

Table 5 Performance of number of RA-supported joints by US in the diagnosis of rheumatoid arthritis

RA-supported	AUC	SE	P	95% CI
Erosion	0.694	0.081	0.021*	0.536–0.853
Doppler	0.775	0.075	<0.001**	0.628–0.922
Synovim>2mm	0.998	0.004	<0.001**	0.000–1.000
Total (because of the three findings)	0.992	0.008	<0.001**	0.000–1.000

AUC, area under curve; CI, confidence interval; RA, rheumatoid arthritis; US, ultrasound; *Significant; **Highly significant.

Table 6 Diagnostic characteristics of suggested cutoff points for the number of RA-supported joints by US in the diagnosis of RA

RA-supported joints	Sensitivity (%)	Specificity (%)	PPV (%)	PNV (%)	DA (%)
Synovium>2 mm ≥ 1 joint	100.0	90.0	87.0	100.0	94.0
Synovium>2 mm ≥ 2 joints	95.0	100.0	100.0	96.80	98.0
Total ≥ 1 joint	100.0	83.30	80.0	100.0	90.0
Total ≥ 2 joints	95.0	96.70	95.0	96.70	96.0

DA, diagnostic accuracy; PNV, predictive negative value; PPV, predictive positive value; RA, rheumatoid arthritis; US, ultrasound.

Table 7 Correlation between anti-CCP and the number of RA-supported joints in the RA group

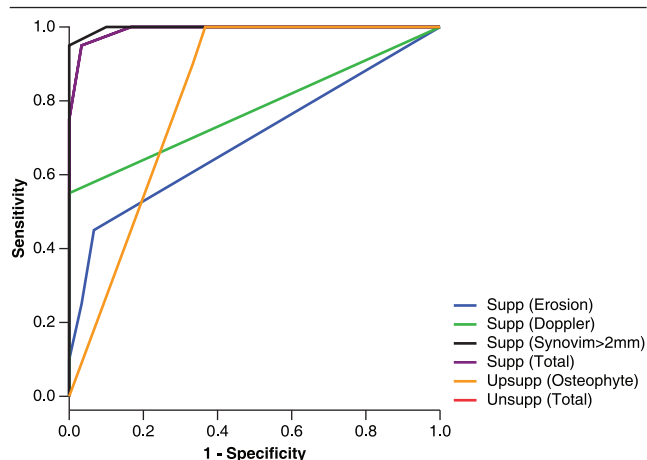| RA-supported joints	r	P
Erosion	0.422	0.064*
Doppler	0.106	0.657
Synovium>2 mm	0.188	0.427
Total	0.181	0.444

CCP, cyclic citrullinated peptide; r, Spearman's correlation; RA, rheumatoid arthritis; *Significant.

Table 8 Correlation between DAS28 and the number of RA-supported joints in the RA group

RA-supported joints	r	P
Erosion	0.237	0.315
Doppler	0.210	0.375
Synovium>2 mm	0.283	0.227
Total	0.234	0.321

DAS, Disease Activity Score; r, Spearman's correlation; RA, rheumatoid arthritis.
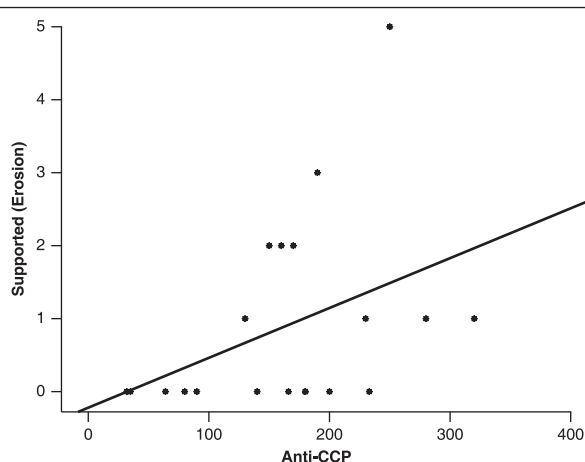
Figure 8

ROC curve for number of RA-supported joints and RA-unsupported joints by US in diagnosis of rheumatoid arthritis

Figure 9

Correlation between anti-CCP and number of joints RA supported (due to presence of erosions) by US in RA group

supported joint) in comparison with the OA group (10.0%) and control (5.0%) group, with no significant difference between the OA and control groups. The number of RA-unsupported joints (because of the presence of osteophytes, absence of synovium more than 2 mm, and absence of positive Doppler signals) was significantly higher in the OA (100.0%) groups than the RA (10.0%) and control (0.0%) groups, with no significant difference between the RA and control groups. This is in agreement with Gary Kunkel *et al.* (2012) who found number of RA-supported jointsin RA groups as follows; 86.0% of patients had at least one RA-supported joint, 20.0% of OA and 6.0% of control groups whereas number of RA-unsupported joints were 100.0% of OA, 23.0% of OA and 12.0% of control groups.

These results showed that an increase in the number of RA-supported joints because of the presence of a total of three findings indicated erosion, abnormal synovium more than2 mm, and a positive Doppler signal, which was significant in the diagnosis of RA; this is in agreement with Kunkel *et al.* [6]. We further studied the RA-supported joints because of the presence of synovium more than 2 mm (alone without erosion or Doppler signals), which was also valid as a high-performance test in the diagnosis of RA.

Cutoff points were verified from the results in our study for the number of RA-supported joints by US in the diagnosis of RA. If one or more RA-supported joints were detected, this scoring system had a sensitivity of 100.0% and a specificity of 83.0%, with a diagnostic accuracy of 90.0% for the diagnosis of RA. If two or more joints were detected, it had a sensitivity of 95.0% and a specificity of 96.70%, with a diagnostic accuracy of 96.0% for the diagnosis of RA. This is in

agreement with the results of Kunkel *et al.* [6], who reported that the Combined Structural/Synovial Score had high sensitivity (95%) and moderate specificity (77%) when RA was defined with one joint classified as 'RA supported'. Moderate sensitivity (73%) and high specificity (97%) were found when more than one joint was classified as 'RA supported' to diagnose RA.

No significant correlation was found between the number of RA-supported joints and DAS28. Interestingly, although this means that the presence of RA-supported joints was unrelated to activity score (in terms of DAS28), it means that it can support the diagnosis of RA patients irrespective of their activity.

Using the semiquantitative scoring system of synovitis by grayscale US, we could measure and grade the examined joints in RA patients as no synovitis, mild, moderate, and severe. On comparing RA patients according to the grade of synovitis, there was no significant difference in the value of DAS28, in agreement with Scheel *et al.* [3], who also reported no significant correlation between their US grading results and the DAS28 score of the patients studied. The presence of nonactive synovitis (synovial thickening and/or effusion without Doppler findings) may not necessarily reflect active disease.

Whereas minimum RI by Doppler was significantly lower in RA patients with severe than moderate synovitis, this finding in our study is in agreement with that of Terslev *et al.* [22], who compared quantitative and qualitative information (including RI) obtained by Doppler US measurements of the wrist joints and the small joints of the hand with the information obtained by postcontrast MRI by assessing the thickness of enhanced synovium (in mm) together with the degree of synovial

inflammation on postcontrast MRI (by semiquantitative scoring) and correlated the imaging results with clinical observations in patients with RA. They found that estimates of synovial inflammatory activity by Doppler US and postcontrast MRI were comparable as assessment of synovial inflammatory activity by the RI in their study indicated lower values of RI in the presence of more severe inflammation detected by MRI.

Estimation of synovial inflammatory activity by the RI appears to be a promising method of detecting and monitoring inflammatory activity in patients with RA.

There was a positive correlation between anti-CCP values and the number of RA-supported joints due to the presence of erosions that was very close to significance but did not reach it ($p = 0.064$). This is in partial agreement with the results of Bongi *et al.* [24], who studied 54 RA patients and found that anti-CCP are highly associated with severe bone lesions in RA, specially bone erosions, and also in agreement with Kim *et al.* [25], who carried out a retrospective study on 216 established RA patients; the extent of joint damage was assessed from plain radiographs using a modified version of the Larsen method, and the results showed that anti-CCP-positive patients had higher joint damage scores than the anti-CCP-negative patients. They concluded that anti-CCP positivity was correlated significantly with more severe joint erosion.

Conclusion

The combined structural and synovial hand joint scoring system used in this study showed high performance in distinguishing RA from OA and controls, but there was no correlation with activity. More studies on a larger scale are needed to verify the validity of this system in establishing the diagnosis of RA.

Acknowledgements

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