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Baseline Synovial Blood Flow Signals in Very Early Rheumatoid Arthritis is Associated with Joint Inflammation and Radiographic Joint Damage

Hamada S Ahmad[1], **Osama Kombar**[2], **Ibrahim Shady**[3*], **Reham M Shaat**[1] **and Gamal Othman**[4]

[1]*Rheumatology and Rehabilitation Department, Mansoura Faculty of Medicine, Mansoura University, Egypt*

[2]*Radiodiagnosis Department, Mansoura Faculty of Medicine, Mansoura University, Egypt*

[3]*Public health and community medicine department, Mansoura Faculty of Medicine, Mansoura University, Egypt*

[4]*Biochemistry department, Mansoura Faculty of Medicine, Mansoura University, Egypt*

[*]**Corresponding author:** Ibrahim Shady, Public health and community medicine department, Mansoura Faculty of Medicine, Mansoura University, 35516, Mansoura, 35516, Egypt, Tel: 96566791792; Fax: 96524916796; E-mail: ebrshady@hotmail.com

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Abstract

Background: Distinguishing which patient with early RA is to run a severe disease course with development of erosions and which is not at baseline evaluation is a major challenge in the management of RA.

Objectives: To assess the changes of the blood flow signals in a total of 2 the studied joints from the start and after one year as well as to predict the future joint damage after one year by assessing the ability of synovial vascularity at baseline measured by power Doppler ultrasound (PDUS).

Patients and Methods: This study was conducted on 34 consecutive early RA patients naive to DMARDs and glucocorticoids who underwent clinical, laboratory, radiologic and ultrasonography (US) assessment at baseline, and 1 year. The degree of US synovial proliferation (US-SP) was investigated in 28 joints using gray-scale ultrasonography. Synovial vascularity was investigated using PDUS and were scored on a 4-grade scale, and the total of the scores in the 28 joints was regarded as the total signal score (US-TSS).

Results: The PD-TSS and US-SP correlated with DAS28-CRP, CRP and radiographic score and to a lesser extent with TJC, SJC and VAS-pain at baseline and one year. PD-TSS and US-SP significantly correlated with HAQ at baseline but not one year. In univariate analysis, the total radiographic score at 1 year and radiographic progression were significantly associated with baseline presence of anti-CCP, presence of RF, US-SP, PD-TSS, radiographic score and the count of joints that had been persistently swollen for the year follow up period. The baseline parameters identified by logistic regression as an independent predictive factor of radiographic score at 1 year and radiographic progression were PD-TSS and radiographic score.

Conclusion: Radiographic score after 1 year and radiographic progression was predicted by baseline synovial vascularity and baseline radiographic score of joint damage. Degree of synovial vascularity and synovial proliferation as measured by ultrasonography are correlated with rheumatoid activity.

Keywords: Rheumatoid arthritis; Synovial vascularity; Radiographic damage; Disease activity

Introduction

Rheumatoid arthritis (RA) is traditionally considered as the prototype of destructive arthritis. Joint destruction in RA often begins very early and progresses rapidly within the first years from symptoms onset [1]. Studies on very early RA (≤ 3 months from symptom onset) have shown that up to 20% of the patients already present with erosions at baseline [1,2].

Preventing joint damage is the ultimate aim of current and novel therapies and treatment strategies in RA. Therefore, distinguishing which patient with early RA is to run a severe disease course with development of erosions and which is not at baseline evaluation is a major challenge in the management of RA. Conventional radiography remains the mainstay for evaluation of RA patients. Although bony erosions and subluxations can be demonstrated in advanced disease [3,4], yet in the early stages of the disease there may be no changes, or may demonstrate non-specific changes.

Angiogenesis represents a major event in promoting the rheumatoid synovitis, offering the necessary blood supply as well as the access of the cellular populations with pro-inflammatory functions [5]. Angiogenesis of the synovial membrane is the primary pathogenic mechanism responsible for the invasive behavior of rheumatoid pannus with subsequent invasion and resorption of underlying cartilage and bone [6,7]. Angiogenesis is not only central to the formation and progression of pannus, but is also an extremely early event in RA [8]. Power doppler ultrasound (PDUS) can detect synovial blood flow which is a sign of increased synovial vascularization. Measuring the synovial baseline inflammatory status and degree of vascularity seems to be the best predictive marker of future joint damage [9].

The aim of the study is to assess the blood flow signals in a total of 28 joints at baseline and after one year and to evaluate its relation with the inflammatory parameters with the disease and to assess the ability of synovial blood flow signals at baseline measured by PDUS to predict the future joint damage after one year.

Patients and Methods

The study is a comparative observational study that was conducted during the period of November 2010 to March 2013. The study was carried in specialized hospitals that deal with management of rheumatoid arthritis cases in Kuwait.

Inclusion criteria included all patients suffering from very early (within 3 months from onset) undifferentiated arthritis (i.e. swelling in 2 or more joints revealed on physical examination without a definite diagnosis in a patient who had never been treated with any disease modifying anti-rheumatic drug (DMARD) [10,11]) attending the outpatient clinics of the hospitals sharing in this study.

The first consecutive 100 patients with undifferentiated arthritis were selected and underwent a clinical, laboratory, and PDUS evaluation at the start of the study and after one year.

Both verbal and written consent were obtained from every patient prior to inclusion in this study after approval of this study from local Ethical Committee.

Clinical assessment

Clinical evaluation was performed for all patients by the same rheumatologist, who was blinded to the US and radiographic findings. The following data were recorded for each patient at study entry: age, sex and symptom duration. Drugs received for RA were recorded at each visit and patients who received DMARDs or corticosteroids were excluded from the study.

At each visit, 28 joints including bilateral glenohumeral, elbow, wrist, Metacarpophalangeal (MCP), Proximal Interphalangeal (PIP), and knee joints were assessed for tenderness and swelling for each patient. A global pain intensity visual analog scale score (VAS pain) was also assessed. Disease Activity Status (DAS) was assessed using DAS28-C Reactive Protein (CRP) tool [12]. Functional disability of each patient was assessed by the HAQ [13].

The patients were followed through the 1st year every one month for clinical evaluation of the patients' conditions for excluding those not meet or lost the inclusion criteria for this study.

All patients were reassessed for diagnosis after one year. Only the data of the patients who scored>6 points based on ACR/EULAR 2010 classification criteria for RA [14] within a period of 1 year follow up and were still naive for DMARDs and glucocorticoids were analyzed.

Laboratory assessment

Blood samples were withdrawn from every patient to measure erythrocyte sedimentation rate (ESR) measured by the Westergren method, serum CRP levels (quantitative assay of CGRP kit was supplied by turbox© CRP, Orion Diagnostica), anti-cyclic citrullinated peptide antibodies (CCP) measured using a third generation ELISA kit (QUANTA Lite® CCP3 IgG ELISA, INOVA Diagnostics, Inc. San Diego, CA, USA), and rheumatoid factor (RF) (measured by Latex fixation test).

Ultrasonography examination

Ultrasonography (US) and power Doppler ultrasound (PDUS) examinations, at baseline and after one year were performed by a single experienced operator who was blinded to the clinical and laboratory findings using high-sensitivity ultrasound equipment (Acuson S2000, Siemens Medical Solutions, USA) with 9L4 linear vascular probe features Multi-D technology for improved imaging and operate from 4-9MHz.

PDUS was performed in each of the 28 joints. All ultrasonic scans were carried out according to the EULAR guidelines [15].

	PDUS	**Gray-scale**	
Score	degree of synovial vascularity	synovial proliferation	effusion
0	Absence of PDUS signal	Absent	Absent
1	Single vessel dots	Slight	Present
2	Confluent vessel dots over less than half the area of synovium	Moderate	
3	Confluent vessel dots over greater than half the area of synovium	Intense	

Table 1: Ultrasonic scores.

The investigator sat in front of the subject for investigation of wrists, MCP and PIP joints. The subject sat with the hand on the thigh, with supination for the volar scans, and with pronation for the dorsal scans in neutral position of the wrist.

For the PDUS examination of the elbows, the sonographer sat in front of the subject. The subject sat with full extension of the elbow and supination of the lower arm for the anterior scans, and for the posterior scans the hand is placed on the hip or on the thigh of the patient (flexion of the elbow joint in a 90° angle) with moderate internal rotation of the humerus. For shoulder scans, patient sat with elbow flexed 90° and the hand should be positioned in supination on top of the patient's thigh.

For investigation of knees the patient was placed supine for the anterior scans (of suprapatellar, lateral and medial recesses) and prone for the posterior scans with the knee joint in neutral position.

PDUS for joint synovium was evaluated, first, by selecting the region of interest that included the joint space, bony margins of the forming bones and a variable view of surrounding tissues. Second, PDUS calibrations parameters were adjusted at the maximum

sensitivity settings, so, pulse-repetition frequency was to lowest (500 to 800 Hz). The Doppler frequency range was set to attain the highest resolution, so, was higher for the study of small joints and superficial tissues, and lower for deep structures especially the knee, the Power Doppler gain was set just below the level that causes the appearance of noise (spill over) artefact. In order to obtain the best image quality, modification of the machine settings (for example, pulse-repetition frequency, gain, steering) was meticulously performed to confidently score each image separately.

The degree of vascularity at various sites of the synovial membrane was scored using a 4-grade scale (range 0-3) (Table 1) [16]. The score at the site with the strongest finding in each joint was adopted as the score of the joint. For each patient the total of the scores of the 28 joints was summed to obtain the total signal score (PD-TSS) [17]. Gray-scale US was used to detect synovial proliferation and effusion. These pathological changes are scored as shown in Table 1 [18].

Radiographic assessment

Volunteer radiologists who were unaware of the clinical and ultrasound findings measured structural damage of the 28 joints at baseline and at 12 months. Radiologic damage was assessed according to the modified Larsen method [19]. The six stages of joint damage progression are defined as shown in Table 2. The score ranges from 0 to 140.

Score	Description
0	Normal
1	Soft tissue swelling and/or joint space narrowing/subchondral osteoporosis
2	Erosions with destruction of the joint surface (DJS)
3	DJS 26-50%
4	51–75%
5	>75%

Table 2: The modified larsen scoring system for assessment of joint damage.

Statistical analyses

All statistical analyses were performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ±standard deviation (SD). A binary logistic regression model was used to determine relevant independent prognostic baseline variables that predict the radiologic outcome after one year. To run binary logistic regression analysis, the modified Larsen radiographic score and radiographic progression variables were dichotomized into qualitative variables: higher or lower than the median value for the total modified Larsen radiographic score at 1 year, and presence or absence of radiographic progression seen on radiography. Univariate analysis of the relation between all baseline values a1 year and radiographic progression was performed. Logistic regression model was used to determine relevant independent prognostic variables. The prognostic variables included in the logistic regression model were selected from results of the univariate analysis. The correlations were assessed by Pearson correlation co-efficient test. The US intra-observer reliability was evaluated using the unweighted kappa test and the overall agreement (defined as the percentage of observed exact agreements) for the grade of power Doppler signal in each joint. Kappa values<0.40 reflect poor agreement, values 0.40-0.75 reflect fair to good agreement, and values>0.75 reflect excellent agreement [20]. p-values<0.05 were considered to be of statistical significance (Figure 1).

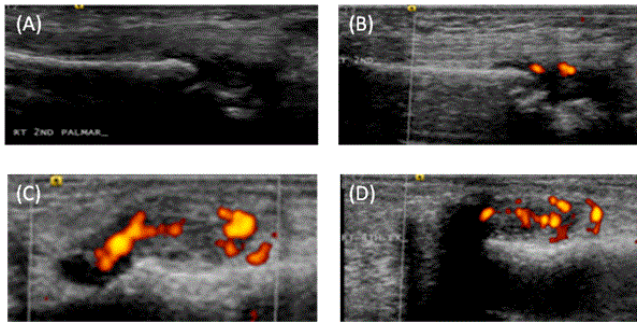

Figure 1: Power Doppler US images of synovitis findings in some of our patients. (A) A longitudinal US image of the palmar surface of the right 2nd metacarpophalangeal joint showed cortical irregularity with synovial thickening (grade2) and mild joint effusion. (B) A longitudinal image of the palmar side of the right 2nd MCP joint, with synovial thickening and proliferation (grade 2) and showed mild hyperemia with power Doppler technique (grade 2). (C) An oblique image of the dorsal side of the right 2nd MCP joint, with synovial thickening and proliferation (grade 2) and showed moderate hyperemia with power Doppler technique (grade 2). (D) A transverse image of the dorsal side of the right 4th MCP joint, with synovial thickening and proliferation (grade 3) and showed marked hyperemia with power Doppler technique (grade 3).

Results

Intra-observer reliability of the US examination was evaluated by recording representative images of the 28 joints of 20 patients (10 from the baseline visit and 10 from the 1 year visit). The recorded images were blindly read and scored for power Doppler signal by the same sonographer a minimum of 3 months after the corresponding real-time scanning. Intra-observer kappa values for the US evaluation of each joint ranged from 0.87 to 1 (mean ± SD=0.94 ± 0.4).

From the 100 subjects enrolled in the study, only 34 patients scored >6 points based on ACR/EULAR 2010 classification criteria for RA within a period of 1 year follow up and were still naive for DMARDs and glucocorticoids. Only the data of these 34 patients (28 females and 6 males) were analyzed. Their mean age was 46.3 ±9.6 years (range 24-65 years) and their disease duration was 6.9 ± 0.7 weeks (range 3-12 weeks). The patient's clinical, laboratory, and radiologic characteristics are shown in Table 3. Seven patients (20.6%) had joint erosions on plain x-ray (scored 3 points according to modified Larsen in at least one joint) at baseline while at the end of one year 28 (82.4%) patients had erosions in at least one joint (data not shown).

The correlations of the US parameters with disease activity indices, HAQ, laboratory and radiographic score are shown in Table 4. The strongest PD-TSS and US-SP correlations were with DAS28-CRP and CRP at baseline and one year. The PD-TSS and US-SP were also

significantly correlated with TJC, SJC and VAS-pain. The PD-TSS and US-SP are significantly correlated with radiographic score at baseline (p=0.018 and 0.010 respectively) and one year (p<0.001). PD-TSS and US-SP were significantly correlated with HAQ at baseline (p=0.030 and 0.026 respectively). In contrast the US indices did not correlate significantly with HAQ at one year.

In univariate analysis, the total radiographic score at 1 year and radiographic progression were significantly associated with the following baseline parameters (Table 5): positivity for anti-CCP, positivity for RF, US-SP, PD-TSS, radiographic score and the count of joints that had been persistently swollen for the year follow up period.

The most important baseline parameters identified by logistic regression as an independent predictive factor of total radiographic score at 1 year were PD-TSS (OR=5.833, 95% CI=1.298-26.223) and radiographic score (OR=4.643, 95% CI=1.057-20.385) after adjustment for the persistent SJC, positivity for anti-CCP and positivity for RF. The radiographic progression was predicted also by baseline PD-TSS (OR=5.120, 95% CI=1.140-22.999) and baseline radiographic score (OR=4.500, 95% CI=1.017-19.902) (Table 6).

	At baseline		**After 1 year**	
	Range	Mean ± SD	Range	Mean ± SD
TJC	4-20	12.9 ± 4.3	4-28	15.9 ± 7.2
SJC	2-17	7.2 ± 4.5	3-25	9.1 ± 5.6
VAS-pain (mm)	10-70	45.4 ± 15.9	20-90	51.3 ± 14.6
DAS28-CRP	0.4-5.6	3.4 ± 1.2	2.5-8.2	5.9 ± 1.5
CRP (mg/dl)	0.9-22.5	8.8 ± 6.8	4.2-30.1	13.8 ± 8.3
ESR (mm)	30498	46.7 ± 23.4	20-150	88.7 ± 36.2
Anti CCP ab positivity	19 (55.9%)			
RF positivity	23 (67.6%)			
US findings				
Effusion joint count	4-12	7.8 ± 2.4	14-21	16.2 ± 1.7
US-SP	4-30	14.9 ± 7.3	17-44	31.8 ± 7.9
PD-TSS	4-30	13.8 ± 8.3	22-64	40.4 ± 13.8
Radiographic score	11-49	26.2 ± 8.6	24-106	51.4 ± 18

Table 3: Clinical, laboratory, US and radiologic findings of the patients at baseline and after 1 year.

	PD-TSS				**US-SP**			
	At baseline		**After 1 year**		**At baseline**		**After 1 year**	
	r	**P**	**r**	**P**	**r**	**P**	**r**	**P**
TJC	0.36	0.037	0.393	0.021	0.349	0.043	0.385	0.025
SJC	0.355	0.039	0.369	0.032	0.411	0.016	0.43	0.011
VAS-pain	0.343	0.047	0.35	0.042	0.346	0.045	0.375	0.029
DAS28-CRP	0.437	<0.001	0.458	<0.001	0.417	0.014	0.441	<0.001
HAQ	0.372	0.03	0.297	>0.05	0.381	0.026	0.268	>0.05
CRP	0.588	<0.001	0.641	<0.001	0.529	<0.001	0.623	<0.001
ESR	0.273	>0.05	0.232	>0.05	0.255	>0.05	0.226	>0.05
Radiographic score	0.405	0.018	0.534	<0.001	0.436	0.01	0.565	<0.001

Table 4: Correlation of PD-TSS with inflammatory parameters and radiographic score at baseline and after 1 year.

	Radiographic score after 1 year		**Radiographic progression**	
Baseline variables	P	OR (95% CI)	P	OR (95% CI)
TJC	0.595	1.024 (0.937-1.119)	0.964	1.005 (0.816-1.237)
SJC	0.485	1.046 (0.922-1.186)	0.688	1.062 (0.792-1.423)
Persistent SJC	0.013	1.110 (1.022-1.206)	0.023	1.155 (1.020-1.308)
VAS-pain	0.123	1.323 (0.927-1.889)	0.224	1.368 (0.826-2.266)
DAS28-CRP	0.099	1.622 (0.913-2.883)	0.366	1.091 (0.903-1.319)
HAQ	0.261	0.409 (0.086-1.945)	0.932	0.998 (0.960-1.038)
CRP	0.131	1.083 (0.977-1.201)	0.114	0.135 (0.011-1.619)

ESR	0.179	1.017 (0.992-1.042)	0.279	1.326 (0.796-2.210)
CCP	0.027	1.004 (1.000-1.008)	0.029	1.142 (1.013-1.287)
RF	0.047	1.243 (1.003-1.540)	0.036	1.248 (1.015-1.534)
US Effusion joint count	0.072	1.101 (0.991-1.222)	0.096	1.361 (0.946-1.957)
US-SP	0.036	1.085 (1.005-1.171)	0.041	1.126 (1.010-1.262)
PD-TSS	0.024	3.795 (1.192-12.084)	0.006	3.506 (1.433-8.579)
Radiographic score	0.035	5.667 (1.129-8.454)	0.007	4.147 (1.479-11.628)

Table 5: Baseline predictive factors of radiographic outcome at one year.

	B	S.E.	OR	95% CI
Baseline predictive parameters for radiographic score				
PD-TSS	1.764	0.767	5.833	1.298-26.223
Radiographic score	1.686	0.76	4.643	1.057-20.385
Baseline predictive parameters for radiographic progression				
PD-TSS	1.633	0.766	5.12	1.140-22.999
Radiographic score	1.504	0.579	4.5	1.017-19.902

Table 6: Logistic regression analysis of predictive factors of total radiographic score at 1year and radiographic progression.

Discussion

The leading cause of joint destruction in RA is the cumulative burden of the local inflammation within the joint, hence predictive factors of radiographic progression may be searched within variables associated with the severity of joint inflammation and its persistence over time. Many efforts are being made in the search for markers able to identify radiographic outcome since the earliest stages of the disease, but results are often conflicting. Discrepancies are probably due to differences between study designs.

In this study we investigated the predictive factors of radiographic outcome in early RA patients who were still naive to DMARDs and glucocorticoids. The main findings of this study are (a) in regression analysis only baseline PD-TSS and baseline radiographic score are associated with the radiographic score after one year and radiographic progression, (b) at baseline and after one year PD-TSS and US-SP are significantly correlated with CRP, DAS28-CRP and radiographic score.

In our study, the baseline radiographic score was found to be a strong predictor of the radiographic score after 1 year and of radiographic progression. Forslind and colleagues, who followed 379 patients with early rheumatoid arthritis (disease duration<1 year) for two years, the independent predictive factor of final radiographic score was baseline radiographic score [21]. In the study by Jansen et al., who enrolled 130 patients with early RA, the baseline radiographic score, was correlated with radiographic progression at 1 year [22].

PDUS was used to assess the synovial vascularity at baseline and values were used to correlate with radiographic progression by many studies. Results have been however conflicting. In our study, logistic regression analysis identified the baseline US-TSS as a strong predictor of the radiographic score after 1 year and of radiographic progression whereas US-SP is correlated with the radiographic score after 1 year and of radiographic progression in univariate analysis. PDUS vascularity and synovitis were previously found to correlate well with the amount of joint damage progression [23,24]. However, other studies [25-27] found that baseline PDUS had not been consistently associated with radiographic outcomes. In contrast to patients enrolled in the current study who were naive to DMARDS or corticosteroids, the different therapeutic regimens prescribed for the patients during the follow-up may explain the lack of baseline predictors in these studies.

Clinical evaluation of synovitis through swollen and tender joint counts remains the cornerstone of the quantitative assessment of inflammation in RA. SJC have repeatedly been shown to be associated with joint damage progression [28-30]. The relationship between the amount of initial joint inflammation and the persistence of inflammation itself, however, is not so evident [31]. Accordingly, there are conflicting results concerning the predictive value of a single assessment of SJC for radiographic damage. In the long-term study by Kaarela [32], the SJC was an independent predictive factor of radiological progression. This association was either weaker [28] or not confirmed in more recent studies [1,33,34]. The crucial importance of joint assessment to predict radiographic outcomes in patients with RA is further highlighted by more recent evidences showing that joint damage progression is driven by residual swollen joints [35]. In our study, the TJC and SJC at baseline did not correlate with radiographic score after one year, however persistent JSC is predictive of the radiographic score in these joints in univariate analysis.

In our study, the baseline anti-CCP antibodies positivity and FR positivity were correlated with radiographic score after 1 year and with radiographic progression in univariate analysis. The predictive value of the anti-CCP antibodies had already been suggested in short-term [21,22,36,37] and also in long-term [38] studies. Many long-term studies [32,39] reported an association between the RF and the radiologic outcome.

Baseline CRP and ESR did not correlate with the radiographic score after one year nor with radiographic progression. CRP and ESR are only indirectly linked to synovitis. The acute phase proteins are primarily produced by hepatocytes in response to interleukins released during inflammation [40]. The predictive value of ESR and, to a lesser extent, of CRP for radiographic progression has been proposed in several independent studies [33,39], but their value in predicting

radiologic outcome appears overall poor [41]. Although there is a link between inflammation and the development of joint damage it is well established that damage may progress in spite of decreased inflammatory activity, and erosions may develop in patients who have few clinical signs of inflammation [42].

In agreement with Naredo et al. [23], we found a strong significant correlation at baseline and one year between the gray-scale score for synovial proliferation and the synovial vascularization index obtained by PDUS and indices of RA inflammatory activity such as DAS28-CRP and CRP serum level and to a lesser extent with VAS-pain, SJC and TJC. On the other hand, although the correlation between the US-TSS and US-SP and HAQ score was significant at baseline, this correlation becomes insignificant at one year. This discrepancy may indicate that in early RA, functional status is more likely related to inflammatory activity whereas as the disease progresses HAQ score indicates either disease activity or residual structural joint damage [23].

The results of this study reflect the pathogenic destructive role of angiogenesis in the rheumatoid synovium. Therefore, the detection of vascularization in early rheumatoid synovial proliferation by PDUS could be considered a strong predictor of disease aggressiveness, which would contribute to making treatment decisions.

Conclusion, radiographic score after 1 year and radiographic progression was predicted by baseline synovial vascularity and baseline radiographic score of joint damage. Degree of synovial vascularity and synovial proliferation as measured by ultrasonography are correlated with rheumatoid activity.

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