Original Paper

Musculoskeletal Ultrasound in Early Rheumatoid Arthritis - Correlations with Disease Activity Score

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ABSTRACT: Purpose: to assess synovial inflammation using musculoskeletal ultrasonography, in a cohort of patients with early rheumatoid arthritis, and establish the correlations with disease activity score. **Material and methods:** We enrolled 29 patients diagnosed with early RA, according to ACR-EULAR 2010 classification criteria, in Rheumatology Clinic, Emergency County Hospital Craiova, between September 2013-August 2014. We performed clinical evaluation, assessed laboratory tests and performed US for all the patients. Musculoskeletal ultrasonography was performed using an ESAOTE MyLab 25 ultrasound, by the same examiner, with multi-frequency linear array transducers (7-12Mh). The presence of synovitis was assessed both in grey scale (GSUS) and power-Doppler (PDUS), according to OMERACT-EULAR consent. **Results:** Assessment of synovial inflammatory activity by ultrasound examination, using both grey scale and PDUS, has shown active synovitis in all patients, with a mean number of joints with active synovitis of 5. Evaluating the grade, using PDUS, we found grade 1 in all patients, 2 in 14 and grade 3 in 3 patients. Inflammatory markers correlated significant with both GSUS and PDUS. Analysis of correlation between GSUS examination parameters and disease activity score, found a positive, moderate inter-relation, results found also for PD score. **Conclusion:** our results sustain the role of US for detecting inflammatory activity in early RA patients, and, in addition with clinical and biological assessment, represents a sensitive, reliable and reproducible method, easily approached, that should be included in our routine evaluation

KEYWORDS: early rheumatoid arthritis, ultrasonography, disease activity score

Introduction

Rheumatoid arthritis (RA) a chronic, autoimmune, inflammatory disease, characterized by progressive joint damage, event that begins from the first weeks of evolution [1]. The primary site of inflammation is represented by synovial membrane, and in early stages, the first alteration is constituted by synovial inflammation, followed by consecutive synovial proliferation, associated with increased vascularization and angiogenesis, start point in pathogenesis of rheumatoid arthritis [2, 3]. Therefore, assessment of synovial inflammation is essential in order to enable the therapeutic measures, appreciate the outcome, evaluate response to treatment and achieve remission, the current aim of RA treatment [4].

Synovitis has been traditionally assessed, indirectly, by evaluating inflammatory markers and clinical examination [3]. Also, in daily practice, composite indices are used to assess disease activity, considering tender and swollen joints, visual analog scale by physician and patient, erythrocyte sedimentation rate and/or C-reactive protein [5-7]. These indices however, may have some disadvantages and miss accuracy due to increase subjectivity in patients with associated depression or fibromyalgia, joint deformities that can interfere with tender and swollen joint count etc. [8-11]. Imaging techniques, such as magnetic resonance imaging (MRI) and musculoskeletal ultrasonography (US) have an increasingly important contribution in evaluation and monitoring such patients [3]. Although it has been proven that has a strong correlation with histological data and provides a predictive value in structural joint damage, MRI is rather expensive, time consuming, not always available for routine examinations and difficult to reproduce [12, 13]. US, by its increased degree of resolution due to high-frequency transducers, constitutes a reliable and compulsory method to diagnose and monitor RA patients. Unlike MRI is relatively cheap, available and can be used as many times as necessary during patient examination, improving the exactitude of clinical examination [14-16]. Both grey-scale and power Doppler ultrasonography are extensively used to detect synovial inflammation and appreciate disease activity, in addition to clinical and laboratory data, in order to apply the proper therapeutic measures, monitor the patients and assess the outcome [15, 17].

The aim of the study was to assess synovial inflammation using musculoskeletal ultrasonography, in a cohort of patients with early rheumatoid arthritis, and establish the correlations with disease activity score.

Material and methods

We enrolled 29 patients diagnosed with early RA, according to ACR-EULAR 2010 classification criteria, in Rheumatology Clinic, Emergency County Hospital Craiova, between September 2013-August 2014, . All the patients signed the informed consent and the study was approved by the Local Ethic Committee.

We performed clinical evaluation, assessed laboratory tests and performed US for all the patients. Evaluation included recording of age, sex, body mass index, medical history and symptoms duration. Clinical examination assessed 28 joints (glenohumeral, elbow, wrist, metacarophalangeal-MCP, proximal interphalangeal-PIP of the hands and knees) for tenderness and swelling. Global pain intensity was assessed by the pateint and doctor, using visual analog scale score, range 0-100mm. Functional status was evaluated using Health Assessment Questionnaire (HAQ) [18] and disease activity by calculating 28-Disease Activity Score (DAS) [19], with 4 variables and simplified disease activity score (SDAI)[20]. Laboratory assessment included serum inflammatory markers (erythrocyte sedimentation rate-ESR and C-reactive protein-

CRP), rheumatoid factor-RF, anti-cyclic citrullinated peptide antibodies-CCP and usual biological analysis.

Musculoskeletal ultrasonography was performed using an ESAOTE MyLab 25 ultrasound, by the same examiner, with multi-frequency linear array transducers (7-12Mh). The presence of synovitis was assessed both in grey scale (GSUS) and power-Doppler (PDUS), according to OMERACT-EULAR consent [21].

GraphPad Prism 5.5 program was used for statistical analysis. Data were presented as mean ±standard deviation (mean±SD). We compared groups using T-test and calculated Pearson coefficient for establishing correlations. A p value less than 0.05 was considered statistically significant.

Results

Our cohort included 29 consecutive patients, diagnosed with early rheumatoid arthritis, with a duration of the symptoms <1 year, diagnosed with early RA, with a duration of the symptoms under 12 months, 25 (86.20%) women and 4 men, with a mean age of 48.97±9.72 years. Analysis of the inflammatory profile, recorded a mean ESR of 30.41±10.88 mm/h and a CRP that ranged from 0.53 to 3.1 mg/dl, with a mean of 1.180± 0.4933. RF was present in 72.41% of the cases (21) and anti-CCP antibodies in 58.62% (17 cases). All the data for the patients are exposed in Table 1.

Table 1: General characteristics of the patients

	N	Mean	CI 95%	SD	Median	Min	Max
Sex(women)(N; %)	25 (86.20)	-	-	-	-	-	-
Sex (men)(N; %)	4 (13.80)	-	-	-	-	-	-
Age (years)	29	48.97	44.78-53.15	10.99	51	21	65
Weight (kg)	29	59.21	61.2-82.9	14.65	47	43	92
Height (cm)	29	156.81	161.0-171.2	11.21	167	153	172
ESR (mm/h)	29	14.28	11.74-16.82	6.154	28.00	20.00	70.00
CRP (mg/dl)	29	1.180	0.39-0.42	0.49	1.100	0.5300	3.10
RF (UI/ml)	29	40.12	26.69-53.54	33.24	32.00	5	23
Anti-CCP	29	118.4	67.90-236.6	129.0	45.00	3.000	375
NAD	29	7.93	2.70-3.98	2.28	8.00	4.00	15.00
NAT	29	3.75	2.83-4.68	2.43	4.00	0	10.00
VAS	29	52.76	47.89-57.62	12.79	50.00	30.00	100.00
DAS28(4v)	29	5.11	4.87-5.34	0.61	5.12	3.81	6.02
HAQ	29	1.24	1.05-1.43	0.49	1.00	0.70	2.80

Evaluating disease activity, we found a mean DAS28 (4v) of 5.11± 0.61; 15 patients (51.72%) had a high disease activity and 14 (48.27%) patients a moderate disease activity. The

disability index, calculated using health assessment questionnaire (HAQ) had a mean value of 1.31±0.53, limits 0.7-2.8.

Assessment of synovial inflammatory activity by ultrasound examination, using both grey scale and PDUS, has shown active synovitis in all patients (Fig. 1a), with a mean number of joints with active synovitis of 5 (limits between 1 and 12). Evaluating the grade, using PDUS, we found grade I in all patients, II in 14 and grade 3 in 3 patients (Fig. 1b).
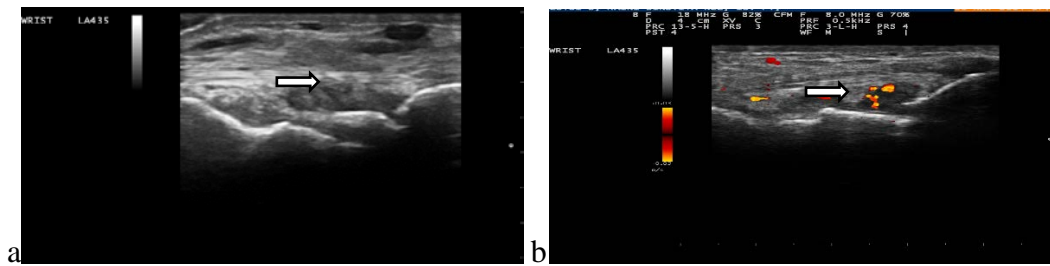

Fig.1. a.GSUS synovitis grade 3; b. PDUS synovitis grade 2, PD grade 2

Analysis of these findings depending on disease activity, we found a mean number of 6.93±1.33 joints with active synovitis in patients with a high disease activity score, whereas for patients with a moderate disease activity the mean was 5.21±1.85, difference statistically significant, p=0.007 (Fig. 2). Also, regarding PDUS, for the 15 patients with high disease activity, the mean number of joints with PD grade 1 synovits was 6.26±1.28, grade 2 0.66±0.69; grade 3 was found in 3 patients, for 2 in one joint and for one in 2 joints. The 14 patients with a moderate disease activity had 4.57±2.02 joints with PD grade 1 synovitis and 0.50±0.62 with PD grade 2 synovitis.
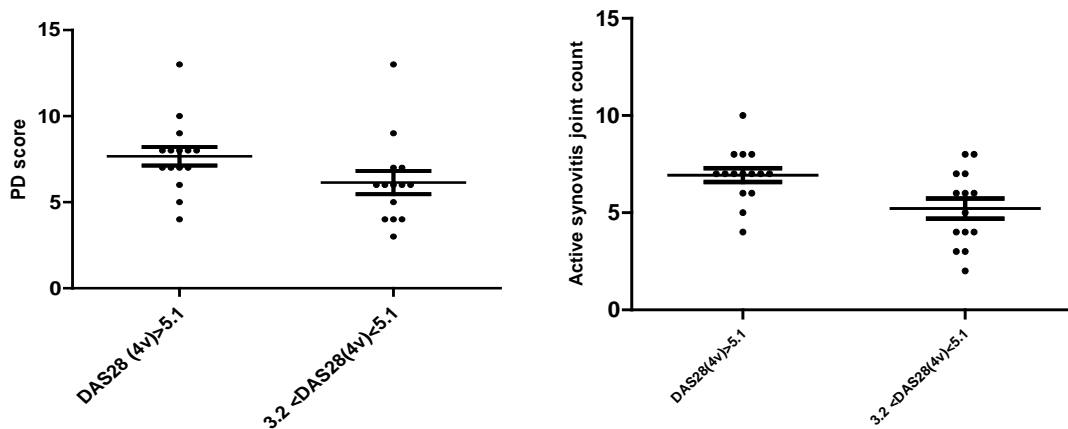

Fig.2. GSUS/PDUS findings depending on DAS28(4v)

Inflammatory markers correlated significant with both GSUS and PDUS, with a Pearson correlation coefficient of 0.598, p=0.0006 for ESR/GSUS; 0.5917, p= 0.0007 ESR/PDUS and 0.654, p=0.0001 CRP/GSUS; 0.5995, p= 0.0006 CRP/PDUS (Table 2).

Analysis of correlation between GSUS examination parameters and disease activity score, found a positive, moderate inter-relation, p=0.453, CI 95% 0.104 to 0.703, statistically significant, p=0.013. For PD score, we also found a positive correlation, r= 0.427, p= 0.020 (Table 3, Fig.3). Regarding disability index, HAQ, the correlation coefficient was 0.32 (p=0.03)/0.41 (p=0.10) (GSUS/PDUS).

Table 2: Correlations between GSUS/PDUS and inflammatory markers

	ESR			CRP		
	r	p	95% CI	r	p	95% CI
GSUS	0.598	0.0006	0.29-0.79	0.6549	0.0001	0.37-0.82
PDUS	0.591	0.0007	0.28-0.78	0.599	0.0006	0.29-0.79

Table 3: Correlations between GSUS/PDUS and DAS28(4v)

	DAS 28(4v)		
	r	p	95% CI
GSUS	0.453	0.013	0.10-0.70
PDUS	0.427	0.020	0.07-0.68
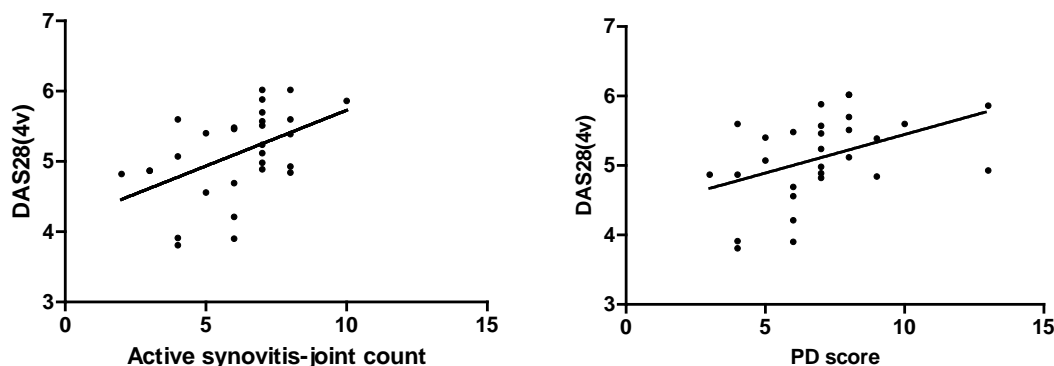
Fig.3. Correlations between GSUS/PDUS-DAS28 (4v)

Discussion

Rheumatoid arthritis is a chronic, autoimmune disease, characterized by systemic inflammation, with progressive joint damage, events that begin from the first weeks of evolution. The primary site of inflammation is represented by synovial membrane, and, in early stages, the first alteration is constituted by synovitis, followed by consecutive synovial proliferation, associated with increased vascularization and angiogenesis, the start point in pathogenesis of rheumatoid arthritis [1-3]. These findings constituted the start point of assessing the direct relationship between synovial vascularization and joint inflammatory activity [4]. In daily practice, several composite indices are used to evaluate disease activity, considering tender and swollen joint count, visual analog scales by patient and physician, inflammation markers, but, sometimes, they can have a lower accuracy due to associated fibromyalgia, depression, deformities that influence joint count etc [8-11]. Imaging methods, such as musculoskeletal ultrasonography or magnetic resonance, are precise, more sensitive and reproducible than clinical evaluation in assessing joint inflammation [14-17]. Moreover, US can be used as often as required during patient examination, improving the exactitude of clinical data.

We studied a cohort of 29 patients, diagnosed with early RA, using both GSUS and PDUS, as US variables that indicate disease activity. US examination has shown active synovitis in all patients, with a mean number of joints with active synovitis of 5 (limits between 1 and 12). Evaluating the grade, using PDUS, we found grade 1 in all patients, 2 in 14 and grade 3 in 3 patients. Similar US findings, of estimating local inflammation and activity, have been reported by several studies [3, 15, 22-24]. We found a significant correlation between inflammatory markers, ESR (with a mean value of 30.41 ± 10.88 mm/h) and CRP (mean value 1.180 ± 0.493 mg/dl), and both GSUS (moderate r=0.598, p= 0.0006 for ESR and r= 0.654, p=0.0001 for CRP) and PDUS (moderate p= 0.5917, p= 0.0007 for ESR and r= 0.5995, p= 0.0006 for CRP). Also *Scire et al* [22] reported, in 2009, a positive, moderate correlation, statistically significant, between inflammatory markers and both active synovitis count and the synovial vascularization index, obtained by PDUS, on a cohort of 106 early RA. Moreover, our findings are in consistency with several previous reports, as the one published *Naredo et al*, in 2007 [3], on a group of 42 early RA patients, *Naredo et al* in 2005 [15], *Terslev et al* [25] and *Hameed et al* in 2008 [26]. This results sustain the general accepted concept that PD is a marker of active synovitis, directly inter-related with inflammatory activity [15, 22, 26].

The report published by *Scire et al* [22], also stated a significant correlation between DAS 28(4v) and US examination, both GS and PD, results reported by several other recent trials, as the one published in Arthritis&Rheum, in 2009, by *Bachaus et al* [27], *Watanabe et al* in 2012

[28], in Clinical Rheumatology, *Naredo et al* in 2007, Arthritis&rRheum [3], etc. [14, 29-31]. Our results show a positive, moderate inter-relation, for both GSUS (p=0.47, statistically significant, p=0.009), and PDUS score (r= 0.4279, p= 0.0206), in agreement with previous studies.

Several scientific reports have concluded that angiogenesis, reflected by vascularization in early RA synovial proliferation, has a pathogenic destructive role [1-3], reflecting the importance of PDUS as a strong predictor of disease evolution and an important tool for therapeutic decisions.

Conclusions

Our results sustain the role of US for detecting inflammatory activity in early RA patients, and, in addition with clinical and biological assessment, represents a sensitive, reliable and reproducible method, easily approached, that should be included in our routine evaluation, in order to enable therapeutic decisions in early RA patients and obtain remission, the current aim of the treatment.

Acknowledgement

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