

THE "JOINT CRITERIA" FOR FIBROMYALGIA DIAGNOSIS IN RHEUMATOID ARTHRITIS PATIENTS: VALIDATION AND ASSESSMENT OF DISEASE ACTIVITY

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Abstract

The objectives of this study were to validate the "joint criteria" for fibromyalgia (FM) diagnosis represented by the difference between tender joint count (TJC) and swollen joint count (SJC) in rheumatoid arthritis (RA) patients undergoing biological treatment and examine clinical and ultrasound parameters in patients with and without FM.

Patients and methods. RA patients on biological treatment were included during one month. ROC analysis was used to determine whether the "joint criteria" could differentiate between patients with associated FM and those without. The disease activity score in 28 joints (DAS28) was calculated and ultrasound (US) examination was performed using the 7 joint score.

Results. 39 patients were included. The "joint criteria" had a sensitivity of 85% and specificity of 87% for FM diagnosis for a difference of ≥ 6 between TJC and SJC. Nine (23%) patients were diagnosed with FM using these criteria. Patients with RA-FM had higher values compared to RA for the DAS28 (5.1 vs 3.3, $p = 0.01$), TJC (12 vs 3, $p < 0.001$) and patient global assessment (PGA) (58 vs 41, $p < 0.001$), but similar values for SJC (1 vs 2, $p = 0.6$), erythrocyte sedimentation rate (ESR) (27 vs 22, $p = 0.21$), C reactive protein (CRP) (8.6 vs 8.4, $p = 0.6$) and ultrasound parameters (Gray Scale synovitis 2.6 vs 3.8, $p = 0.9$; Power Doppler synovitis, 1.2 vs 1.6, $p = 0.5$; Gray Scale Tenosynovitis 0.4 vs 0.3, $p = 0.3$; Power Doppler Tenosynovitis, 0.3 vs 0.2, $p = 0.08$).

Discussions. Our findings confirm previous published data on RA-FM diagnosis and disease characteristics on a sample of RA patients on biological treatment. The "joint criteria" is a feasible tool and could easily identify patients with RA and FM in order to improve disease management.

Conclusions. A difference of ≥ 6 between TJC and SJC is diagnostic of FM in RA patients. Patients that satisfy this criteria have higher DAS28 scores, TJC, PGA but similar SJC, ESR, CRP and US scores compared to RA patients without FM.

Keywords: rheumatoid arthritis, fibromyalgia, joint criteria, ultrasound

INTRODUCTION

Fibromyalgia (FM) is a common comorbidity in patients with rheumatoid arthritis (RA), with an estimated prevalence of 10-20% (1,2). RA treatment goal is to achieve remission or low disease activity and it is guided by a treat-to-target algorithm. This algorithm takes into account the disease activity scores (DAS), which are important in RA treatment decisions (3). Patients with RA and concomitant FM (RA-FM) exhibit higher disease activity scores because of higher subjective variables such as tender joint count (TJC) and patient global assessment of disease activity (PGA) compared to RA patients, but similar erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (4), leading to improper assessment of treatment response. Also, patients

with RA-FM exhibit higher fatigue, disability and worse quality of life compared to RA patients (1).

Patients with RA-FM are less likely to achieve remission both on synthetic and on biological DMARDs because of persistent pain, and not because of inflammation (5,6). Recently, a cross-sectional study found that biological treatment use was higher among patients with RA-FM compared to patients with RA (7). This study raised the concern that the more frequent biological use in patients with RA-FM compared to RA patients is due to persistence of non-inflammatory pain and not inflammation. Hence, it is important to identify RA patients associated FM and make treatment decisions considering this comorbidity.

FM diagnosis is difficult since no validated biomarker exists and it is based solely on clinical judge-

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ment. The 1990 Classification Criteria for FM require the presence of chronic pain in all four quadrants of the body and over 11 tender points at manual palpation (8). Tender point count is difficult to standardize and is not routinely performed in patients with RA. Pollard et al. (2) proposed that the diagnosis of FM in RA patients can be made when the difference between tender joint count and swollen joint count is ≥ 7 with a sensitivity of 83% and a specificity of 80%.

Ultrasonography (US) is superior to clinical examination in terms of sensitivity and specificity of detecting synovitis in patients with RA (9). Synovial proliferation and vascularisation can be assessed by use of Gray scale US (GSUS) and Power Doppler US (PDUS). Several US scores for assessment and monitoring RA activity have been proposed and validated in recent years (10–14). The US score that uses 7 joints (US7) proposed by Backhaus et al (14) has proven its validity and sensitivity to change, reflecting therapeutic response (15). This score evaluates synovitis/tenosynovitis and erosions in a semi-quantitative way at 7 selected joints of the hand and foot. US, especially PD US, has proven its superiority in the assessment of disease activity in patients with RA and FM compared to clinical evaluation and use of disease activity scores (16,17).

OBJECTIVES

To determine whether the difference between tender joint count and swollen joint count ("joint count criteria") could differentiate between RA and RA-FM patients and to evaluate clinical and US parameters in RA patients undergoing biological therapy with or without concomitant FM according to the "joint criteria".

PATIENTS AND METHODS

This cross sectional study was performed during a one month period in our rheumatology department. RA patients on stable biological treatment (> 6 months) were consecutively enrolled. Patients with associated Sjogren syndrome, chronic hepatitis C and hand osteoarthritis were excluded. The study was approved by the local Ethics Committee and all patients signed the informed consent.

Clinical assessment

Demographics and disease characteristics were retrieved from patients charts. All patients under-

went clinical assessment and TJC, swollen joint count (SJC), PGA on a 100 mm visual analogue scale were used to calculate the DAS28. ESR and CRP were measured on the same day. Rheumatoid factor and anti citrullinated protein antibodies (ACPA) positivity were recorded from charts at the moment of biological treatment initiation. ACPA antibodies were not assessed for all patients who started biological treatment prior to 2012. All patients filled in the Health Assessment Questionnaire (HAQ) disability index.

Ultrasound examination

US was performed by an experienced sonographer on an Acuson S2000 (Siemens Healthcare), equipped with a linear high frequency probe (18 MHz). The sonographer was blinded to clinical evaluation. PD settings were made according to recommendations (18): filters were kept at the lowest setting and gain was lowered until noise disappearance.

In order to evaluate synovitis, tenosynovitis and erosions the US7 score proposed by Backhaus et al was used (14). This US score evaluates 7 joints from the dominant hand and foot: wrist, second and third metacarpophalangeal and proximal interphalangeal, and second and fifth metatarsophalangeal joints. Synovitis and synovial/tenosynovial vascularity are scored semiquantitatively (grade 0-3) by GS and PD ultrasound. Tenosynovitis and erosions were scored for presence.

Synovitis was assessed at wrist and hand joints on the dorsal, ulnar and palmar side and feet joint only on the dorsal side. A total of 13 PDUS and 9 GSUS images were examined for each patient. The scoring range is 0–27 for GS synovitis, 0-39 for PD synovitis, 0-7 for GS tenosynovitis (GS TS), 0-21 for PD tenosynovitis (PD TS), and 0-14 for erosions.

Fibromyalgia diagnosis

FM diagnosis was considered positive if patients met the 1990 Classification criteria for FM and we assessed whether the "joint criteria" i.e. the difference between tender joint count and swollen joint count (TJC-SJC) could identify patients with FM.

Statistical analysis

The statistical analysis was performed with SPSS version 21. Shapiro-Wilk test was performed to check for normality of distributions. Comparisons across groups were performed with the student T test

for normal distributed data and Mann Whitney U for those not following normal distribution. Differences between proportions between groups were calculated with the Chi square test. ROC curve and ROC curve analyses was used to determine the area under the curve and the sensitivity and specificity of the "joint count criteria" for FM compared to the 1990 Classification criteria for FM. A statistical significance level of $p < 0.05$ was used.

RESULTS

Thirty-nine patients were included, 77% women, mean age 55.2 ± 11.3 years, mean disease duration 15.25 ± 9.4 years. Patient demographics and disease characteristics are presented in Table 1. FM diagnosis was positive for 7 (18%) patients according to the 1990 Classification Criteria for FM.

TABLE 1. Demographic and disease characteristics of included patients

Variable		RA patients n = 39
Age (years)		55.2 (11.3)
Body mass index (kg/m ²)		26 (4)
Ever smoker		13(33)
Education (years)		11 (4)
Comorbidities	Ischemic heart disease	8 (20.5)
	Thyroid dysfunction	4 (10.3)
	Diabetes	4 (10.3)
Disease duration (years)		16 (9)
Biological treatment duration (years)		5 (4)
Rheumatoid factor positivity		33(84.6)
ACPA	Positive	8 (20.5)
	Negative	16 (41)
	NA	15 (38.5)
DMARD treatment	Methotrexate	18 (46)
	Leflunomide	16 (41)
	Sulphasalazine	8(20)
Radiological stage	1	1 (2.6)
	2	16 (41)
	3	17(43)
	4	5 (12.8)

Data are expressed as mean (SD) or n (%)

ACPA – anti-citrullinated protein antibody; NA – not assessed

The area under the curve for diagnosing FM with the "joint criteria" (TJC-SJC) compared to 1990 Classification criteria for FM was 0.82, p value 0.008, 95% CI 0.65 – 1 (Fig. 1). ROC analysis showed that a cut-off value of ≥ 6 for the TJC-SJC "joint criteria" for diagnosis of FM can discriminate with a sensitivity of 85% and a specificity of 87% between RA and RA-FM patients.

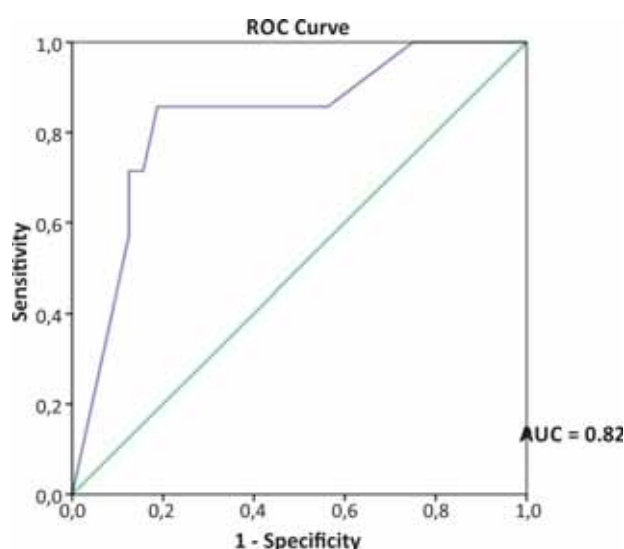


FIGURE 1. Receiver operating curve (ROC) curve for Tender Joint Count- Swollen Joint Count criteria for diagnosis of fibromyalgia

Nine (23%) out of 39 patients were classified as having associated FM by using the FM joint criteria. Patients with RA-FM were significantly older compared to RA patients. Disease duration, demographic and treatment were comparable between groups (Table 2).

TABLE 2. Demographic and disease characteristics of RA and RA-FM patients

Variable	RA n = 30	RA-FM n = 9	p value	
Age (years)	53.1 (11.6)	61.8 (6.7)	0.03	
Disease duration (years)	15.4 (9.8)	17.6 (10.3)	0.6	
Ever smoker	11 (36.7)	2(22.2)	0.7	
Biological treatment duration (years)	5 (3.8)	6.8 (5.6)	0.4	
Body Mass Index kg/m ²	26.1 (3.7)	26.9 (6.3)	0.9	
Education (years)	11 (4,20)	12 (4,17)	0.07	
Early retirement	13 (43.3)	3 (33.3)	0.5	
Rheumatoid factor positive	25 (83.3)	8 (88.9)	0.6	
ACPA	negative	11 (36.7)	5 (55.6)	0.4
	positive	6 (20)	2 (22.2)	
	NA	13 (43.3)	2 (22.2)	
Radiological stage	2	14 (46.7)	2 (22.2)	0.4
	3	12 (40)	5 (55.6)	
	4	3 (10)	2 (22.2)	
	DMARD treatment	Methotrexate	16 (53.3)	
	Leflunomide	11 (36.7)	5 (55.6)	0.3
	Sulphasalazine	5 (16.7)	3 (33.3)	0.09

Data are expressed as mean (SD) or n (%); NA – not available;

DMARD – disease modifying anti-rheumatic drugs

Figure 2 shows the number of patients with RA and RA-FM on different biological drugs.

Significantly higher values for TJC, patient global assessment (PGA), DAS28 were found in the RA-FM group, with no differences for SJC or inflamma-

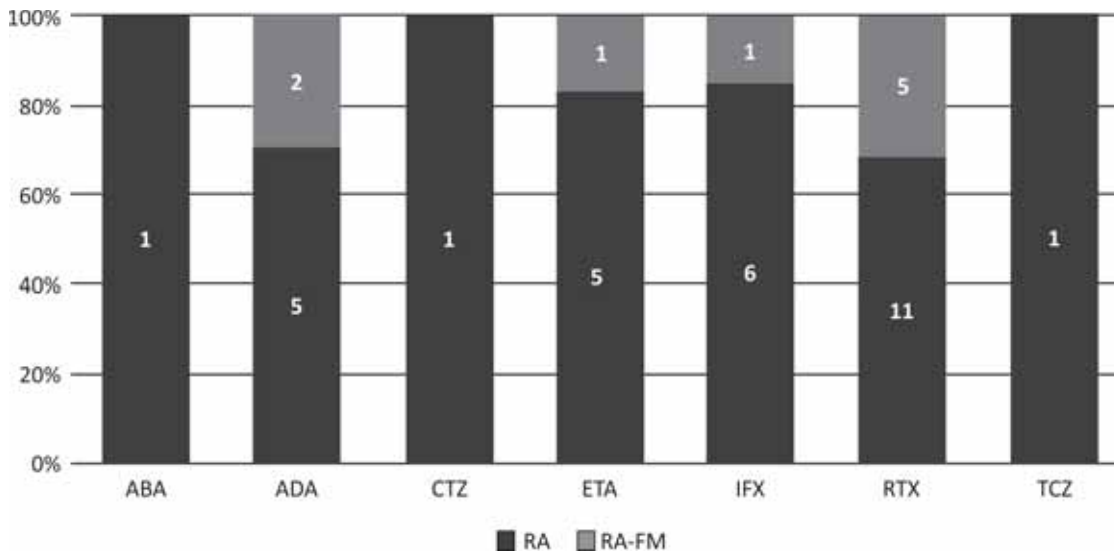


FIGURE 2. Type of biological treatment of RA and RA-FM patients

ABA – abatacept, ADA – adalimumab, CTZ – certolizumab pegol, ETA – etanercept, IFX – infliximab, RTX – rituximab, TCZ – tocilizumab

tory markers (ESR, CRP). GS and PD-US7 scores were similar between groups (Table 3).

TABLE 3. Clinical and US findings in RA and RA-FM groups

Variable	RA (n = 30)	RA-FM (n = 9)	p-value
PGA (mm)	41.33 (18.2)	58.88 (17.6)	<0.001
TJC	3 (0-10)	12 (9-17)	<0.001
SJC	2 (0-7)	1 (0-6)	0.54
ESR (mm/h)	22 (18)	27(16)	0.21
CRP (mg/l)	8.4 (17)	8.67 (9)	0.66
DAS28CRP	3.33 (0.98)	5.13 (1.18)	0.01
HAQ score	1.03	1.5	0.01
GS synovitis	3.8(4.3)	2.6(1.6)	0.9
PD Synovitis	1.6(2.9)	1.2 (1.2)	0.5
Erosions	3.7(2.7)	4.8(2.8)	0.2
GS TS	0.3 (0.8)	0.4(0.7)	0.3
PD TS	0.2(1.1)	0.3(0.7)	0.08

Data are expressed as mean (SD)

PGA – patient global assessment; TJC – tender joint count; SJC – swollen joint count; ESR- erythrocyte sedimentation rate; CRP – C reactive Protein; DAS28 – disease activity score in 28 joints; HAQ – health assessment questionnaire; GS gray scale; PD-power Doppler; TS – tenosynovitis

DISCUSSION

A difference of ≥ 6 between TJC and SJC can discriminate between RA-FM and RA patients with high sensitivity and specificity. Although a previous study found a different cut-off value (of ≥ 7) for TJC-SJC being diagnostic for FM with similar sensitivity and specificity (2), our study confirms that this criteria can be used for the diagnosis of FM in patients with RA. The 1990 Classification Criteria for FM use tender point examination, which is not stan-

dardized and require extra time for consultation during the visit. The "joint criteria" have the advantage of being in the core set of clinical parameters that clinicians use to evaluate RA patients.

A cut-off of ≥ 6 or ≥ 7 joints difference between the tender and the swollen joint count could be used to differentiate between RA and RA-FM, but previous studies suggest that FM in RA is a disease continuum and patients that do not satisfy diagnostic criteria have fibromyalgic features (19). In the context of higher TJC than SJC, irrespective of the scale of this difference, in the presence of fibromyalgic features, treatment should be approached with a focus on exercise, psychological counseling and pain medication, besides immunosuppression.

DAS28 scores were higher in patients on biological treatment with RA-FM compared to RA patients. While variables of the DAS28 linked to inflammation (ESR, CRP, SJC) were similar between the two groups, variables with a non-inflammatory component of pain (TJC, PGA) were higher in the RA-FM group compared to the RA group. US7 GS, PD and erosions scores were similar between the two groups. This finding underlines the fact that while inflammation, reflected by the presence of synovitis, is similar between the two groups, DAS28 scores are significantly higher in patients with RA-FM diagnosed with the "joint criteria". Several previous studies found similar findings and it seems that non-inflammatory pain caused by central sensitization mechanisms characteristic for FM determine these differences in clinical parameters between patients with

RA and RA-FM (2,4,20,21). FM presence may also influence treatment decisions, as a recent study has found (22). Using the "joint criteria" to identify RA patients with possible associated FM is feasible and it could help clinicians in treatment decision-making.

This is the first study in Romania to evaluate the "joint criteria" as possible criteria for diagnosis of FM in RA patients. The impact of FM diagnosed with the "joint criteria" on the clinical examination using US as reference, in a group of RA patients on biological treatment, was also evaluated for the first time.

Although various diagnostic criteria for FM were used, FM prevalence in RA was similar in previous studies. By using a score higher than 8 on the regional pain scale and higher than 6 on a visual analogue scale for fatigue, a 17.1% prevalence of FM was found (1). Ranzolin et al (4) found a slightly lower prevalence of FM in RA patients, of 13.4%, by employing the 1990 Classification Criteria for FM. The higher prevalence of RA-FM found in our study of 23%, compared to 12% and 17% found by Pollard et al by using the "joint criteria" *in the two cohorts they studied* could be explained by our study population. All our patients were on biological treatment and it has been proven that biological treatment use is higher among patients with RA-FM (7).

Patients with RA-FM had a DAS28 mean score in the high disease activity range although on stable biological treatment. Patients with RA-FM have higher DAS28 scores and their chances of reaching remission are lower compared to RA patients (5,6).

US7 scores were similar for synovitis, tenosynovitis and erosions between the RA-FM and RA group. Previous studies have proven that US performs better than clinical examination in the evalua-

tion of RA-FM patients. One study used the US7 score in a case-control study on patients with RA-FM and RA to demonstrate that US synovitis scores are not affected by FM in RA patients. Also, PD-US7 was superior to GS-US7 in assessing disease activity in patients with RA-FM (16). In one of our previous studies we also found that US is superior to clinical evaluation in patients with RA-FM by examining the 28 joints included in the DAS28 score (17).

The main limit of this study is the small sample of patients included, larger sample sizes might find different cut-offs for the "joint criteria" for FM diagnosis in RA. Also, we did not assess anxiety and depression which are frequent among patients with RA and might influence clinical parameters (23). We did not perform US examination in a temperature-controlled environment, which might influence PD-US results (24).

Future studies should confirm whether using the "joint criteria" and US monitoring of disease activity prospectively in patients with RA-FM could influence treatment decisions. Also, there is need for interventional studies in order to assess the impact of FM treatment in RA patients and how it may influence disease outcomes.

CONCLUSIONS

A difference of ≥ 6 between TJC and SJC in patients with RA is diagnostic for associated FM with a sensitivity of 85% and specificity of 87%. Patients with RA and FM according to the above stated definition have higher disability, DAS28 scores, TJC, PGA but similar SJC, ESR, CRP. US7 scores are similar between patients with RA and RA-FM on biological treatment, when FM is diagnosed with the "joint criteria".

REFERENCES

1. Wolfe F., Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. *J Rheumatol.* 2004; 31(4):695–700.
2. Pollard L.C., Kingsley G.H., Choy E.H., Scott D.L. Fibromyalgic rheumatoid arthritis and disease assessment. *Rheumatology.* 2010; 49(5):924–8.
3. Smolen J.S., Aletaha D., Bijlsma J.W.J., Breedveld F.C., Boumpas D., Burmester G. et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010; 69(4):631–7.
4. Ranzolin A., Brenol J.C.T., Bredemeier M., Guarienti J., Rizzatti M., Feldman D. et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. *Arthritis Care Res.* 2009; 61(6):794–800.
5. Salaffi F., Gerardi M.C., Atzeni F., Batticciotto A., Talotta R., Draghessi A. et al. The influence of fibromyalgia on achieving remission in patients with long-standing rheumatoid arthritis. *Rheumatol Int.* 2017; 37(12):2035–42.
6. Duran J., Combe B., Niu J., Rincheval N., Gaujoux-Viala C., Felson D.T. The effect on treatment response of fibromyalgic symptoms in early rheumatoid arthritis patients: results from the ESPOIR cohort. *Rheumatology (Oxford).* 2015; 54(12):2166–70.
7. Lage-Hansen P.R., Chrysidis S., Lage-Hansen M., Hougaard A., Ejstrup L., Amris K. Concomitant fibromyalgia in rheumatoid

- arthritis is associated with the more frequent use of biological therapy: a cross-sectional study. *Scand J Rheumatol* 2016; 45(1):45–8.
8. Wolfe F., Smythe H.A., Yunus M.B., Bennett R.M., Bombardier C., Goldenberg D.L. et al. The American College of Rheumatology 1990. Criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990; 33(2):160–72.
 9. Colebatch A.N., Edwards C.J., Østergaard M., van der Heijde D., Balint P.V., D'Agostino M-A. et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013; 72(6):804–14.
 10. Naredo E., Rodríguez M., Campos C., Rodríguez-Heredia J.M., Medina J.A., Giner E. et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2008; 59(4):515–22.
 11. Damjanov N., Radunović G., Prodanović S., Vuković V., Milić V., Pašalić K.S. et al. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: Comparison with DAS-28. *Rheumatology.* 2012; 51(1):120–8.
 12. Vlad V., Berghea F., Libianu S., Balanescu A., Bojinca V., Constantinescu C. et al. Ultrasound in rheumatoid arthritis - volar versus dorsal synovitis evaluation and scoring. *BMC Musculoskelet Disord.* 2011;12:124
 13. Hartung W., Kellner H., Strunk J., Sattler H., Schmidt W.A., Ehrenstein B. et al. Development and evaluation of a novel ultrasound score for large joints in rheumatoid arthritis: one year of experience in daily clinical practice. *Arthritis Care Res (Hoboken)* 2012; 64(5):675–82.
 14. Backhaus M., Ohrndorf S., Kellner H., Strunk J., Backhaus T.M., Hartung W. et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: A pilot project. *Arthritis Rheum.* 2009; 61(9):1194–201.
 15. Backhaus T.M., Ohrndorf S., Kellner H., Strunk J., Hartung W., Sattler H. et al. The US7 score is sensitive to change in a large cohort of patients with rheumatoid arthritis over 12 months of therapy. *Ann Rheum Dis.* 2012;1163–9.
 16. da Silva Chakr R.M., Brenol J.C.T., Behar M., Mendonça J.A., Kohem C.L., Monticelo O.A. et al. Is ultrasound a better target than clinical disease activity scores in rheumatoid arthritis with fibromyalgia? A case-control study. *PLoS One.* 2015; 10(3):e0118620.
 17. Ghib L.J., Tamas M.M., Damian L.O., Felea I., Muntean L.M., Rednic N. et al. The role of ultrasonography in assessing disease activity in patients with rheumatoid arthritis and associated fibromyalgia. *Med Ultrason.* 2015;17(3):339–44.
 18. Torp-Pedersen S., Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. *Ann Rheum Dis.* 2008; 67(2):143–9.
 19. Wolfe F., Michaud K., Busch R.E., Katz R.S., Rasker J.J., Shahouri S.H. et al. Polysymptomatic distress in patients with rheumatoid arthritis: understanding disproportionate response and its spectrum. *Arthritis Care Res (Hoboken)* 2014;66(10):1465–71.
 20. Boyden S., Hossain I., Wohlfahrt A. Non-inflammatory Causes of Pain in atients with Rheumatoid Arthritis. *Curr Rheumatol Rep.* 2016; 18(6):30
 21. Joharatnam N., McWilliams D.F., Wilson D., Wheeler M., Pande I., Walsh D.A. A cross-sectional study of pain sensitivity, disease-activity assessment, mental health, and fibromyalgia status in rheumatoid arthritis. *Arthritis Res Ther* 2015; 17(1):11.
 22. Chakr R.M. da S., Brenol C., Ranzolin A., Bernardes A., Dalosto A.P., Ferrari G. et al. Rheumatoid arthritis seems to have DMARD treatment decision influenced by fibromyalgia. *Rev Bras Reumatol* 2017; 7(5):403–11.
 23. Inanc N., Yilmaz-Oner S., Can M., Sokka T., Direskeneli H. The Role of Depression, Anxiety, Fatigue, and Fibromyalgia on the Evaluation of the Remission Status in Patients with Rheumatoid Arthritis. *J Rheumatol.* 2014; 41(9):1755–60.
 24. Ellegaard K., Torp-Pedersen S., Henriksen M., Lund H., Danneskiold-Samsoe B., Bliddal H. Influence of recent exercise and skin temperature on ultrasound Doppler measurements in patients with rheumatoid arthritis – an intervention study. *Rheumatology.* 2009; 48(12):1520–3.