RHEUMATOID ARTHRITIS ASSOCIATED TO FIBROMYALGIA: FACTORS ASSOCIATED WITH ACTIVE SYNOVITIS AND A PROPOSAL OF AN ALGORITHM FOR MANAGEMENT

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Abstract. Introduction: *Recent studies have shown that ultrasound (US) assessment of disease activity in rheumatoid arthritis (RA) with associated fibromyalgia (FM) before disease-modifying anti-rheumatic drug escalation is primordial. The goal of this study was to assess the correlation between clinical and US disease activity in RA patients with concomitant FM comparatively to RA patients without FM. Specifically, we aimed to identify the predictive factors of detection of active US-synovitis.* ***Methods:*** *We conducted a cross-sectional study that included patients with diagnosis of RA (ACR/EULAR 2010 criteria) with and without concomitant FM (ACR 2016). US-detected synovitis was defined and scored 0-3 using the OMERACT scoring system at the joint level for both grey-scale (GS) and Doppler power (DP). Multiple linear regression analysis was performed, adjusting for clinical and demographic variables.* ***Results:*** *Eighty patients distributed into 40 patients in each group were recruited. No significant difference was observed between the groups regarding mean of the three-variables of Disease-activity-score (DAS28 V3). Multiple linear regression showed that in RA+FM group US synovitis detection was positively associated with male gender (B = 0.29, p = 0.04) and with the DAS28 V3 (B = 0.87, p = 0.014), and negatively associated with the patient global assessment (PGA) (B = -0.49, p = 0.004). Doppler activity was positively associated with the DAS28 V3 (B = 0.51, p = 0.002) and with the physician global assessment (B = 0.55, p = 0.02), negatively associated with the PGA (B = -0.65, p = 0.005).* ***Conclusion:*** *Our study showed that a high DAS28 V3 seems to be significantly associated with active US-synovitis in RA patients with comorbid FM.*

Key words: *fibromyalgia, synovitis, ultrasound, activity*

Introduction

Fibromyalgia (FM) is a chronic rheumatological disease characterized by widespread musculoskeletal pain, fatigue, cognitive problems, and sleep disturbance [1]. Although the incidence of FM is between 2% and 8% in the general population [1, 2], its prevalence in rheumatoid arthritis (RA) patients has been reported to reach 5% to 52% [3]. In recent years, research on RA with concomitant FM has increased and several studies have focused on the impact of this comorbidity on the disease activity assessment [4-6). Indeed, chronic pain and central sensitization in fibromyalgic RA can lead to disconnections between subjective and objective activity parameters, which may falsely increase RA activity scores and lead to over-treatment [3, 6-8]. In fact, the mainstay of RA treatment is the treat-to-target (T2T) strategy, where patients should have their drugs escalated periodically until reaching remission (or low disease activity) according to a clinical composite score, such as the 28-joint Disease Activity Score (DAS28) [9]. If the target is not achieved because of any misinterpretation of the activity measure, both undertreatment and over-treatment could happen [4].

Ultrasound (US) has consistently improved clinical practice in rheumatology in the last decades [10]. US-determined synovitis has been studied as an alternative target versus clinical composite scores [10]. Hence, US as an accessible objective measure, seems to be particularly useful whenever the clinical assessment tends to overestimate disease activity, such as in RA with concomitant FM [10-12]. Previous studies have demonstrated that the Power Doppler (PD) score was particularly useful to assess disease activity in patients with RA and FM [13]. Many US scores have been tested and validated, and the most widely used scoring system for small joints and tenosynovitis is the semi-quantitative EULAR score [14].

The **aim** of this study was to assess the correlation between clinical and US disease activity in RA patients with concomitant FM comparatively to RA patients without FM. Specifically, we aimed to identi-

fy the predictive factors of detection of US-synovitis and Doppler activity.

Methods

Study design

Between January and September 2022, consecutive RA patients diagnosed according to the 2010 ACR/European League Against Rheumatism (EULAR) criteria [15] and treated with conventional DMARDs (cDMARDs) or biological DMARDs (bDMARDs), were recruited at the outpatient clinic of a Tunisian tertiary rheumatology center.

The inclusion criteria were an age > 16 years at time of RA diagnosis, a disease duration ≥ 2 years and an active disease (defined by a DAS28-ESR ≥ 3.2). Exclusion criteria were patients with concomitant systemic inflammatory conditions that could intensify synovitis, such as overlap autoimmune syndromes, cancer, and chronic viral infections, patients with endocrine diseases (such as hypothyroidism, hyperthyroidism) that may cause common musculoskeletal symptoms and patients with chronic mood disorders.

All data regarding socio-demographic characteristics, medical history, past and ongoing prescribed medications (including corticosteroids and DMARDs), were obtained from medical records review. The corticosteroids duration and dose (mg/day) at the last visit to the hospital were also determined. RA characteristics including the age at the time of diagnosis, disease duration, rheumatoid factor (RF) positivity (with a positive cut-off value of > 15 IU/mL), anti-cyclic citrulline peptide (anti-CCP) (with a positive cut-off value of > 10 IU/mL), structural damage, and extra-articular manifestations were also registered. Functional disability was assessed using the Arabic version of the health assessment questionnaire – disability index (HAQ) [16].

All patients were screened for concomitant FM by 2016 ACR criteria, which include the Widespread Pain Index (WPI) and a Symptom Severity (SS) scale, the sum of which is used as a measure of FM severity (FS) [17]. An RA age matched control group was included.

Thus, two groups of patients were identified: RA with FM (cases) and RA without FM (controls).

A clinicobiological assessment and an US assessment of RA activity were performed on the same day for each patient.

Clinical and biological assessment

The clinicobiological assessment of RA activity included the patient global assessment (PGA), physician Global Assessment (PhGA), pain Visual Analog Scale (VAS-Pain), morning stiffness duration (MSD), number of night awakenings (NNA), tender joint count (TJC) and swollen joint count (SJC). Fatigue was assessed using a visual analogue scale (VAS-F) ranging from 0 to 100 and the Arabic version of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale [18]. The FACIT-Fatigue scale is a 13-item questionnaire assessing self-reported fatigue and the total score ranges from 0 to 52. For analysis of severity of fatigue, scores were categorized into four grades: composite score 40-52 = little or no fatigue, score: 27-39 = some fatigue, score: 14-26 = quite a lot of fatigue, score: 0-13 = extreme fatigue [17]. FM impact on quality of life was assessed by the FM impact questionnaire (FIQ) [19]. A total FIQ score less than 39 represents a mild impact, between 39 and 59 a moderate impact, and more than 59 a severe impact [18].

The Arabic Hospital Anxiety Depression Scale (HADS) was used to assess depression and anxiety [20]. C-reactive protein (CRP) (normal < 6 mg/l) and erythrocyte sedimentation rate (ESR) at 1 hour (normal < 20 mm/h) were measured. For the purposes of this study, four clinical disease scores were calculated for each patient: The simplified disease activity index (SDAI) [21], the clinical disease activity index (CDAI) [20], the four-variables DAS28 (calculated with ESR value) [8]. We also calculated the three-variables DAS28 (DAS28 V3), which is a validated EULAR scale for RA, considered to be more objective than the DAS28 as it comprises only three variables (TCJ, SJC and ESR), excluding the subjective component PGA [22]. Both DAS28-ESR and DAS28V3 were computed using the Web-site calculator (http://www.das-score.nl/das28).

Ultrasound assessment

The US examination was performed by a single experienced rheumatologist (with a PhD in US and 5 years of regular practice experience) who was blinded to the presence or absence of FM diagnosis. The US equipment was Esaote MyLAb 60 with a linear transducer of 6-18 MHz. The Doppler frequency was 8.0 MHz; wall filter, pulse repetition frequency ranged from 0.5 to 1.0 MHz and gain fixed at random noise abolishment. US assessment included 22 joints (wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP) bilaterally for every patient) and 15 tendons (9 extensors and 6 flexors of the wrist and hand). We considered the definitions of the Outcome Measures in Rheuma-

tology (OMERACT) Ultrasound (US) working group for ultrasonographic pathologies and elementary lesions of rheumatic disorders [23]. Synovitis was defined as a non-compressible hypoechoic intracapsular area (synovial thickening) and tenosynovitis (TS) as non-compressible hypoechoic tissue within the synovial sheath seen in 2 perpendicular planes [22]. Synovitis and tenosynovitis were defined and scored 0-3 using the PDUS scoring system at the joint level for both grey-scale (GS) and Doppler power (DP) [13].

Statistical Analyses and Sample Size Calculation

The sample size of the RA+FM group required was calculated based on the prevalence of FM in RA reported in the literature [3].

Data were managed and analyzed with the software IBM SPSS Statistics version 11.5 [24].

Quantitative variables were expressed as mean values ± standard deviation minimum and maximum. Categorical variables were indicated as frequencies and percentages.

Comparisons between these three groups were made with the chi-square test or Fisher's exact test (categorical variables) and the Mann–Whitney test (continuous variables).

The correlation between clinical disease activity scores and their ultrasonographic equivalents was evaluated using the Spearman's rho coefficient (r). R-value less than 0.3 was considered poor; between 0.3 and 0.39, moderate; between 0.4 and 0.69, strong; and more than 0.7 very strong. The level of statistical significance was set at 5% ($p \leq 0.05$) in all tests.

In a second time, multiple linear regression analysis was performed, adjusting for clinical and demographic variables. During the regression analysis, all significant variables in the above analysis were input as independent variables and subsequently detection of US synovitis (with GS > 1), Doppler activity and TS were dependent variable.

In order to improve the representativeness of the sample and to minimize the potential for confounding variables, which can bias the multiple regression analysis results [24], we compared weighted sample patients to the Tunisian population suffering from FM on a set of confounding variables identified after a literature review on FM patients characteristics (sex, educational attainment and depression) [1, 2].

Iterative proportional fitting, or raking, which was first introduced by Deming and Stephan [26], was used. The method of raking requires using an iterative proportional fitting procedure under marginal constraints [25]. The marginal population distributions of sex and educational attainment was obtained from a cross section study on demographic characteristics of Tunisian FM patients [27], and lack of Tunisian studies on the prevalence of depression in FM patients, we lied on a similar population, which is the Syrian population [28].

Ethical concerns

The local committee of Mongi Slim hospital Tunisia approved the study (Decision No. 25/2020). A written informed consent was obtained from all patients before any data was collected.

Results

1. Demographic and characteristics of rheumatoid arthritis patients with and without fibromyalgia

Eighty patients distributed into 40 patients in each group were recruited. Epidemiological characteristics and RA characteristics were comparable between groups. Coxitis and atlantoaxial subluxation were significantly more frequent in RA without FM group ($p = 0.006$ and $p = 0.049$ respectively). No significant difference in corticosteroids prescription was found between the groups ($p = 0.88$), nor in cDMARDs prescription ($p = 0.052$). Among the RA with FM group, 52% were treated with biological therapy versus 18% of RA without FM group ($p = 0.04$).

2. Clinical disease activity assessment in rheumatoid arthritis patients with and without fibromyalgia

Mean PGA, mean NNA and mean TJC were significantly higher in RA with FM patients ($p = 0.02$, $p = 0.001$ and $p = 0.004$, respectively). Mean FACIT-F was significantly higher in RA with FM group ($p = 0.001$), with 57% of patients having moderate fatigue. According to the HAD, 46% of patients had probable anxiety and 41% probable depression, when FM was associated with RA and mood disorders were significantly more frequent than in RA without FM group ($p = 0.000$). Mean FIQ was 54.9 ± 24 with half of patients suffering from a high impact of FM.

DAS28 was significantly greater than DAS28 V3 in RA with FM group ($p = 0.001$).

Table 1 summarizes epidemiological characteristics, RA characteristics and treatment in the two groups.

Table 1. Comparison of RA patients with and without fibromyalgia according to demographic, clinical characteristics, disease parameters and current treatment

Characteristics	RA with FM n = 40	RA without FM n = 40	P
Age ± SD (years)	59 ± 9.5	56.9 ± 10.3	0.34
Ratio-Sex	0.05	0.21	0.06
Postmenopausal (n)	28	34	0.34
Married, (n)	27	23	0.9
Education <10 years, n	18	15	0.07
Mean age at the time of diagnosis (years)	45.4 ± 11.4	46.1 ± 8.8	0.056
Disease duration (years)	15.2 ± 7.8	13.4 ± 8	0.42
RF positive, n (%)	27 (70)	29 (72)	0.9
Anti-CCP positive (%)	13 (32)	20 (50)	0.07
Erosive disease, n (%)	34 (83)	27 (69)	0.15
Coxitis, n	1	3	0.006
Atlantoaxial subluxation, n	0	3	0.004
Extra-articular manifestations, n	30	24	0.38
Corticosteroids, n (%)	29 (72)	28 (71)	0.88
Corticosteroids dose (mg/day)	9.1 ± 4.4	8 ± 3,5	0.31
Current conventional DMARD use, n (%)	19 (47)	33 (80)	0.052
Current biologic DMARD use, n (%)	21 (52)	7 (18)	0.04
Mean VAS-Pain ± SD	63.1 ± 18.7	48.2 ± 21.5	0.002
Mean PGA ± SD	59.7 ± 21	48.9 ± 20	0.02
Mean PhGA ± SD	43.4 ± 24.1	42.05 ± 22.3	0.8
Mean VAS-F ± SD	60 ± 23.6	29.1 ± 9.9	0.001
Mean FACIT-F ± SD	27.4 ± 18.7	34.3 ± 8.4	0.001
Mean HAD Anxiety	10.5 ± 3.8	5.26 ± 3.5	0.001
Mean HAD Depression	9.7 ± 4.6	5.18 ± 3.4	0.002
Mean MSD (minutes) ± SD	30 ± 43	24 ± 33.1	0.2
Mean NNA ± SD	1.68 ± 1.2	0.77 ± 1.24	0.001
Mean TJC ± SD	9.8 ± 5.2	6.4 ± 5.3	0.004
Mean SJC ± SD	3.1 ± 2.7	3.5 ± 3	0.24
Mean CRP ± SD (mg/l)	15 ± 15.6	21.6 ± 36	0.8
Mean ESR ± SD (mm/h)	39 ± 22.3	40.9 ± 26	0.9
Mean DAS 28 ± SD	5.2 ± 1	4.8 ± 1.24	0.12
Mean DAS28 V3 ± SD	5 ± 0.9	4.7 ± 1.1	0.14
Mean CDAI ± SD	23.3 ± 9.3	22.4 ± 18.1	0.2
Mean SDAI ± SD	39.4 ± 23	37.1 ± 23	0.5
Mean HAQ ± SD	1.5 ± 0.75	1.15 ± 0.7	0.3

RA: Rheumatoid arthritis, FM: Fibromyalgia, RF: Rheumatoid factor, anti CCP: Anti-citrullinated protein antibodies, DMARD: Disease-modifying antirheumatic drugs, VAS-Pain: Pain Visual Analog Scale, VAS-F: Fatigue Visual Analogue Scale, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, PGA: Patient global assessment, PhGA: Physician Global Assessment, MSD: Morning stiffness duration, NNA: Number of night awakenings, TJC: Tender joint count, SJC: Swollen joint count, HAD: Hospital Anxiety and Depression Scale, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, DAS 28: Four-variable Disease Activity Score in 28 joints, DAS28 V3: Three-variable Disease Activity score in 28 joints, CDAI: Clinical Disease Activity Index, SDAI: Simple Disease Activity Index, HAQ: Health Assessment Questionnaire.

3. Ultrasound disease activity assessment in rheumatoid arthritis patients with and without fibromyalgia

Mean US SJC was significantly higher than mean SJC in both RA with FM (p = 0.003) and RA without FM (p = 0.001) groups. US SCJ was higher in RA without FM group with no statistical significance (5.2 ± 3.6 vs 3.9 ± 3.5, p = 0.06).

The number of joints with GS grade ≥ 1 was significantly higher in RA without FM group than in

RA with FM group (182 vs 55, p = 0.038). No significant difference was noted between the groups regarding US TS parameters: total number of TS (p = 0.168), TS GS US score (p = 0.102) and TS PD US score (p = 0.122). Details of US disease activity assessment parameters in the two groups were summarized in Table 2.

Table 2. Comparison of RA patients with and without fibromyalgia according to ultrasound disease activity parameters

	RA with FM n = 40	RA without FM n = 40	p
US SCJ	3.9 ± 3.5	5.2 ± 3.6	0.06
GS US score	7.5 ± 9.3	9.2 ± 8.3	0.87
PD US score	4.8 ± 8.1	6 ± 7.3	0.162
TS GS US score	4.9 ± 6.47	3.21 ± 5.2	0.102
TS PD US score	3.07 ± 5.6	2.08 ± 4.22	0.122

US: Ultrasound, SCJ: Swollen joint count, TS: Tenosynovitis, GS: Grey scale, PD: Puissance Doppler.

4. Predictive factors of detection of US synovitis, tenosynovitis and Doppler activity in RA patients with and without concomitant FM

Multiple linear regression showed that in RA with FM group US synovitis detection was positively associated with male gender (β = 0.29, p = 0.04), VAS-Pain (β = 0.87, p = 0.014) and with the DAS28 V3 (β = 0.49, p = 0.001), and negatively associated with PGA (B = -0.49, p = 0.04). In RA without FM group, US synovitis was positively associated with SJC (β = 0.837, p = 0.001).

In RA with FM group, PD activity was positively associated with the DAS28 V3 (β = 0.51, p = 0.002) and with PhGA (β = 0.55, p = 0.02), negatively associated with the PGA (β = -0.65, p = 0.005), while it was positively associated with the DAS28 (β = 3.08, p = 0.047) in RA without FM group.

In RA with FM group, detection of US TS was positively associated with the VAS-Pain (β = 0.67, p = 0.006), the PGA (β = 0.62, p = 0.003) and the HAD score (β = 0.39, p = 0.04). However, it was negatively associated with the PhGA (β = -0.87, p = 0.001). US TS was positively associated with the DAS28 (β = 0.46, p = 0.02) and the HAD score (β = 0.79, p = 0.01) in RA without FM group.

Details of Multiple linear regression results were summarized in table 3.

Table 3. Predictive factors of detection of US synovitis, Doppler activity, and tenosynovitis in RA patients with concomitant FM

		β coefficient (95% CI)	p
US synovitis	Sex	0.29 (0.19, 0.49)	0.04
	Age	0.01 (-0.21, 0.16)	0.82
	VAS-Pain	0.87 (0.43, 1.12)	0.014
	PGA	-0.49 (-0.63, -0.01)	0.04
	PhGA	0.35 (-0.14, 0.63)	0.09
	NNA	-0.31 (-2, 0.48)	0.123
	MSD	0.03 (-0.8, 0.09)	0.21
	VAS-F	-0.53 (-0.76, 0.05)	0.46
	FACIT-F	0.23 (-0.2, 0.29)	0.72
	TJC	0.64 (0.14, 0.93)	0.08
	SJC	-0.07 (-0.19, 0.6)	0.71
	FIQ	0.02 (0.01, 0.78)	0.42
	HAQ	-0.57 (-1.37, 0.27)	0.27
	HAD	0.02 (-2.5, 3.02)	0.85
	ESR	0.65 (-0.09, 1.12)	0.08
	CRP	0.4 (-0.04, 0.78)	0.53
	CDAI	0.07 (0.03, 1.14)	0.92
	SDAI	-0.67 (-0.82, 0.94)	0.65
	DAS28	0.57 (-0.91, 1.58)	0.06
	DAS28 V3	0.49 (-0.77, 1.75)	0.001
	Sex	0.42 (-0.82, 2.9)	0.11
	Age	0.2 (-2.7, 1.54)	0.87
Doppler activity	VAS-Pain	0.87 (-0.5, 1.04)	0.06
	PGA	-0.65 (-0.09, 1.12)	0.005
	PhGA	0.55 (0.01, 0.81)	0.02
	NNA	-0.21 (-1.74, 0.49)	0.058
	MSD	-0.32 (-0.41, 0.12)	0.07
	VAS-F	0.31 (0.13, 1.13)	0.8
	FACIT-F	0.33 (-0.13, 0.49)	0.29
	TJC	0.49 (-0.76, 1.24)	0.052
	SJC	-0.06 (-0.9, 0.72)	0.7
	FIQ	0.08 (-0.05, 2.4)	0.8
	HAQ	0.57 (-4.3, 1.6)	0.43
	HAD	0.2 (-2.3, 2.5)	0.87
	ESR	0.73 (-0.12, 1.63)	0.13
	CRP	0.22 (-0.17, 0.93)	0.7
	CDAI	-0.76 (-1.2, 0.65)	0.47
	SDAI	-0.8 (-0.87, 0.11)	0.22
	DAS28	0.23 (-3.07, 4,1)	0.64
	DAS28 V3	0.51 (-0.96, 0.78)	0.002
	Sex	0.12 (0.07, 1.8)	0.45
	Age	0.27 (-1.5, 2.54)	0.07

Continuation of Table 3

US TS	VAS-Pain	0.67 (-0.2, 2.08)	0.007
	PGA	0.62 (0.02, 1.46)	0.003
	PhGA	-0.87 (-4.43, 3.97)	0.001
	NNA	0.24 (-0.11, 0.36)	0.34
	MSD	-0.27 (-1.62, 2.12)	0.32
	VAS-F	0.47 (-0.02, 1.11)	0.052
	FACIT-F	0.39 (-0.26, 1.32)	0.06
	TJC	0.47 (-2.2, 2.24)	0.43
	SJC	0.21 (-0.47, 0.5)	0.9
	FIQ	0.07 (-0.08, 1.3)	0.63
	HAQ	1.4 (-1.3, 3.5)	0.4
	HAD	0.39 (-1.4, 1.86)	0.04
	ESR	0.6 (0.32, 2.3)	0.1
	CRP	0.27 (-1.07, 2.73)	0.3
	CDAI	0.17 (-0.9, 0.42)	0.17
	SDAI	0.13 (-0.43, 0.9)	0.22
	DAS28	0.31 (-2.17, 2.1)	0.09
	DAS28 V3	0.37 (-1.7, 3.09)	0.25

RA: Rheumatoid arthritis, FM: Fibromyalgia, RF: Rheumatoid factor, anti CCP: Anti-citrullinated protein antibodies, DMARD: Disease-modifying antirheumatic drugs, VAS-Pain: Pain Visual Analogue Scale, VAS-F: Fatigue Visual Analogue Scale, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, PGA: Patient global assessment, PhGA: Physician Global Assessment, MSD: Morning stiffness duration, NNA: Number of night awakenings, TJC: Tender joint count, SJC: Swollen joint count, HAD: Hospital Anxiety and Depression Scale, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, DAS 28: Four-variable Disease Activity Score in 28 joints, DAS28 V3: Three-variable Disease Activity score in 28 joints, CDAI: Clinical Disease Activity Index, SDAI: Simple Disease Activity Index, HAQ: Health Assessment Questionnaire.

Discussion

Several studies have demonstrated that chronic pain and central sensitization in fibromyalgic RA can lead to disconnections between subjective and objective activity parameters [6-8]. However, few of them focused on the role of other factors that might interfere with the modulation of pain.

To the best of our knowledge, this is the first study that assessed the predictive factors of detection of US-synovitis and Doppler activity in RA patients with and without FM.

Our study showed that after adjustment for confounding variables, active synovitis on US were positively associated to DAS28 V3 and negatively associated to PGA in RA with FM patients.

The relationship between FM and RA has been widely investigated. In 1983, Wolfe and Cathey for the first time focused the attention on this association [29], while Lee and colleagues revealed that the FM prevalence was higher in RA patients compared to the general population [30]. Over the past decade, researchers have focused on the impact of this comorbidity on RA course, activity assessment and consequently DMARDs prescription. In fact, consistent with our results, previous reports showed that FM inflates subjective RA activity parameters (VAS-Pain, PGA, NNA and TJC), with comparable objective parameters (SJC, CRP, VS) [3, 6, 31, 32]. Indeed, it is not always easy to distinguish between musculoskeletal pain caused by RA or FM, since generalized pain is the hallmark of FM and there are several common symptoms between FM and inflammatory rheumatic diseases (such as fatigue, sleep disturbance and mood disorders) [5]. Thus, TJC and PGA may both be influenced in RA fibromyalgic patients by generalized hyperalgesia, which may result, according to some researchers, from long-lasting nociceptive inputs from inflamed joints, generating peripheral and central sensitization, and increasing sympathetic nervous system activity [33]. In fact, although some studies have shown that in animal models proinflammatory cytokines were implicated in the development of aberrant central pain processing leading to widespread pain sensitivity, in humans the link between inflammation and alterations in central pain processing is not well established [34, 35]. In the other hand, RA patients with increased levels of fibromyalginess were found to share neurobiologic features, which were observed in patients with FM [36].

The results of the multiple linear regression in our study showed that in RA with FM group, US synovitis detection was positively associated with male gender. In other words, men with RA and concomitant FM are more likely than women to have GS-determined synovitis. This result might be explained by two facts: firstly, both RA and FM are known to be more prevalent among females [5, 28]. In our study, women constituted 95% of RA patients with FM versus 80.2% of patients without FM. Similarly, in the study of Shresher at al. [38], 96.3% of the fibromyalgic RA were women. To minimize the potential for this confounding variable (gender) on the multivariate analysis, we proceeded to a sample adjustment by comparing weighted sample patients to the Tunisian population suffering from FM.

Secondly, abundant evidence from several epidemiologic studies clearly demonstrated that gender is an important factor in the modulation of pain [38]. Literature data strongly suggested that men and women differed in their responses to pain: they were more variable in women than men, with increased pain sensitivity and more painful diseases commonly reported among women [39].

Another interesting result of the multiple linear regression in our study was that PGA was negatively associated with the detection of both US synovitis and Doppler activity. In fact, PGA is a subjective parameter that can be influenced by any other comorbidity of the patient. As it is well known, and as shown in our study, all the subjective parameters of disease activity assessment are overestimated when FM is associated to RA. Consequently, disease activity scores which include both subjective and objective parameters, such as DAS28 (4 parameters) were significantly higher in RA with FM patients. Ranzolini et al. [40] compared the DAS28 in RA with FM and RA without FM groups and concluded that this score was 1.33 points higher in FM group, and the results from a multivariate linear model indicated that FM was an independent predictor of the DAS28 associated with a mean adjusted increase of 0.885 points in this score [41].

To minimize the subjective component in the clinical scores, we calculated the three-variable DAS28. No significant difference in this score was noted between the cases and controls groups, however DAS28 V3 was significantly higher than the DAS28 only in RA with FM group. These results might be explained by the persistence of a subjective component in the DAS28 V3, which is the TJC. In fact, TJC is highly over-weighted in the DAS28 score with a coefficient of 0.56 versus 0.28 for SJC [30]. Thus, DAS28 V3 seemed to be a convenient and useful means of assessing disease activity in RA+FM patients. The results of the multiple linear regression analysis in our study supported these findings as in RA with FM group both US synovitis detection and Doppler activity were positively associated with DAS23 V3, while in RA without FM group US detection was directly and positively associated with the SJC and Doppler activity with DAS28.

Hence, our results confirm the disconnection between TJC and SJC only in RA with associated FM and support the dogma of Pollard et al. [6] who suggested that a Δ TJC (TJC-SJC) > 7 was predictive of concomitant FM.

PhGA is a subjective parameter included in CDAI and SDAI scores. In our study, no statistically significant difference was observed in phGA between RA with FM and RA without FM groups. We might explain this result by the implicit conviction of the rheumatologist that RA activity was not ‘‘really’’ higher in fibromyalgic RA patients. Thus, multiple linear regression analysis showed that PhGA was positively associated with Doppler activity detection in RA with FM patients. That is to say, when an authentic high disease activity is suspected by the physician, the probability of Doppler activity detection is high.

TS is a very frequent painful manifestation of RA and may often be mistaken for synovitis [42]. This is the main reason why we included the US examination of tendons in our study. We did not note a significant difference between the groups in US TS parameters: total number of TS ($p = 0.168$), TS GS US ($p = 0.102$) and TS PD US scores ($p = 0.122$). Ghib et al. [11] scanned 12 tendons (extensor ulnari carpis tendon and 1-5 finger flexor tendons) in GS and PD US in both hands. TS GS scores had minimum and maximum values from 0 to 6 for the RA group and 0 to 4 in the RA/FM group, while TS PD scores ranged between minimum and maximum values of 0 to 6 for RA, 0 to 2 for RA/FM [11]. In our study, we scanned 15 tendons (9 extensors and 6 flexors of the wrist and hand). TS GS scores had minimum and maximum values from 0 to 9 for the RA with FM group and 0 to 12 in the RA without FM group, while TS PD scores ranged between minimum and maximum values of 0 to 8 for RA without FM, 0 to 6 for RA with FM.

Detection of US TS was positively associated with the HAD score in both fibromylagic and non-fibromyalgic RA patients, and with VAS-pain and PGA only in FM group. This result suggests that TS seems to be associated with worse patient-reported outcomes as it seems to be a predictive factor of pain worsening and mood disorders. Our results go in line with those of Bellis et al. [42] who aimed to estimate the prevalence of US-detected tenosynovitis in RA patients in clinical remission and to explore its clinical correlates. The study included 427 RA patients in clinical remission. TS and synovitis were scored by US GS and PD semi-quantitative scoring systems at wrist and hand joints. A flare questionnaire (FQ) was used to assess unstable remission. PD TS significantly correlated with two patient-reported outcomes (morning stiffness and FQ), while synovial US findings did not [42]. US TS showed a significant association with the presence of at least mild functional disability, as measured by the HAQ. The authors explained this result by the fact that TS involvement could explain symptoms of the subpopulation of RA patients in clinical remission characterized by mild relapses and unstable remission but not associated with severe RA in terms of disability or damage [41].

To sum up, to the best of our knowledge, this is the first study that studied the predictive factors

of detection of US-synovitis and Doppler activity in RA patients with and without FM. Consequently, we were unable to find in the literature a similar study to compare our results.

We used a semi-quantitative grading system to ensure an accurate comparison of the US scores between cases and controls groups.

We proceeded to a sample adjustment by comparing the weighted sample patients to the Tunisian population suffering from FM to improve the representativeness of the sample and to minimize the potential for confounding variables.

Another strength of our study was that we used the 2016 ACR criteria [17], which are the most specific recent criteria for FM diagnosis. In light of our results and after a deep analysis of literature, we propose the algorithm in Figure 1 when treating RA patients with concomitant FM.

On the other side, we acknowledge that our study did not thoroughly compare groups according to their FM symptoms intensity and duration. Thus, we were also probably including patients with the most severe FM. We also admit other limitations of our study mainly the small sample size of the groups.

Conclusion

This preliminary study has confirmed that the presence of FM in RA patients may affect the subjective variables resulting in higher activity scores and that three-variable DAS28 seems to be a convenient mean of assessing disease activity in these patients. Other factors, such as gender and mood disorders, seem also to interfere with the modulation of pain.

As an accessible objective measure, US stands as a promising tool to complement disease activity assessments in scenarios, in which clinical scores may mislead treatment decisions, as when FM is associated with RA.

As indicating, a US evaluation for every patient is not feasible in many countries, where rheumatologists and US equipment are not readily available, and in the light of our results, we highly recommend to perform a US examination in fibromyalgic RA patients with DAS28 > 3.2, when the patient is male, with a low PGA, high PhGA and high DAS28 V3. Randomized clinical trials and more comprehensive cohort studies are requested to support our findings.

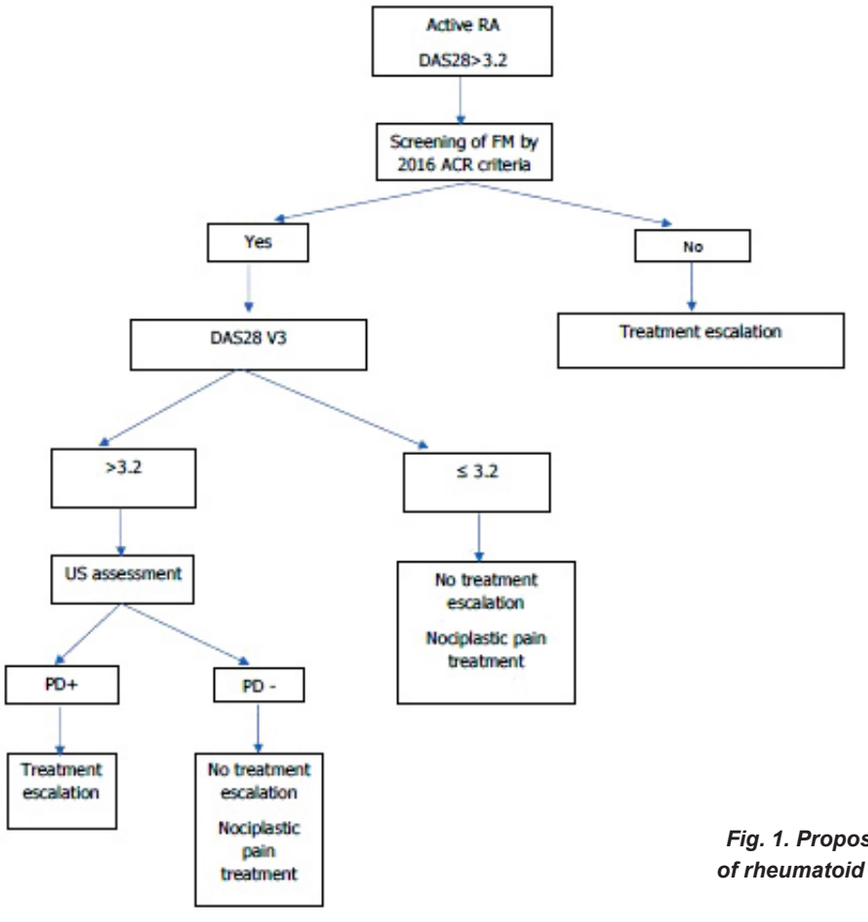

Fig. 1. Proposal of an algorithm for managment of rheumatoid arthritis patients with concomitant fibromyalgia

Acknowledgments: *None*

Data availability statement: *The authors declare that the data supporting the findings of this study are available within the article and its supplementary material. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.*

Conflicts of interest and funding: *The authors declare that there is no conflict of interest. No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.*

Ethical concerns: *The local committee of our hospital approved the study (Decision No. 25/2020). A written informed consent was obtained from all patients before any data was collected.*

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Submitted: 12.02.2024

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