Painless and painful synovitis have similar ultrasound and clinical outcomes: one-year cohort study in longstanding rheumatoid arthritis women patients

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Abstract

Objective

We aimed to compare the painless synovitis evolution with painful synovitis, based on bone erosion by ultrasonography over a year in women with longstanding rheumatoid arthritis. Ultrasound inflammatory measurements and radiographic, functional and clinical findings were also compared between groups at the end of the same follow-up.

Methods

A prospective cohort study was rolled out, involving 60 women with RA, divided into two groups: painless and painful, with 30 patients in each group. The wrist and MCPs joints were assessed by ultrasound and plain x-ray, initially and after 12 months (T0 and T12). There was also a clinical assessment (activity scores, functional tests, disease and treatment progression variables) at 6 and 12 months.

Results

Patients' average age was 58.0±12.8 and average length of disease 16.4±9.8 years. Initially, the demographic characteristics were similar between groups, however, the painful group had worse clinical and functional scores. There were no statistically significant differences in the majority of US bone erosions and US inflammatory measurements, nor in radiographic progression variables between the groups. Over one year, pinch strength test and DAS 28 remained worse in the painful group ($p<0.05$). Clinical worsening variables and change of treatment evolved similarly between the groups, on T6 and T12.

Conclusion

According to the study, the painless group progressed similarly to the painful one over a year, as regards bone erosion, ultrasound inflammatory measurements, radiographic findings, clinical worsening and change of treatment in female longstanding RA patients.

Key words

rheumatoid arthritis, synovitis, pain, ultrasound, radiographic

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Introduction

Inflammatory peripheral arthropathies (PAs) is usually clinically marked by local pain and swelling (1-3). However, some patients with rheumatoid arthritis (RA) may not complain of pain despite the persistent presence of swollen joints, especially patients with juvenile inflammatory arthropathy and long-term disease (4, 5). The presence of synovial hypertrophy (SH) not accompanied by pain may delay the diagnosis of the disease (4), delay the patient's decision to seek medical care, and lead to the disease not being treated. Additionally, the joint inflammation persistent can lead to irreducible and disabling deformities (6).

Pain has been increasingly studied in the management of RA, perhaps because it is the most frequent and debilitating symptom reported by patients. However, the pain symptom may be affected by external factors in addition to synovial inflammation, such as psychosomatic factors and fatigue (7). Moreover, pain may not be correlated with the inflammation in some RA patients and instead be due to a sensitisation mechanism of the central nervous system (8). Despite these factors, pain is often the target for treatment in patients with PAs.

In addition to physical and laboratory tests, some ultrasound (US) tools, such as power Doppler (PD), may aid in clarifying joint inflammatory disease activity. Cartilage and erosion US evaluation provides a good alternative for monitoring disease progression (9-12).

D'Agostino *et al*. suggested US algorithms for monitoring RA treatment and to assist in the early diagnosis or in cases of failure to treatment. These US feasibilities are important in clinical practice (13).

Painless joint swelling in RA patients may lead to doubts concerning disease activity and the management of these patients. Few studies have evaluated painless synovitis in PAs in adults, thus, little is known about the evolution and prognosis of this scenario (14). The aim of this study was to compare the evolution of joint damage by evaluating US measurement of bone erosion in painful synovitis and painless synovitis during a one-year follow-up. synovial hypertrophy (SH) and PD measurements by US and clinical, functional and radiographic variables, as well as disease activity and treatment-related variables, were also compared between these two groups of patients at the end of the same follow-up.

Material and methods

Study design

This was a prospective cohort study involving established RA patients. This study was approved by the Human Research Ethics Committee of the Universidade Federal de São Paulo-UNIFESP (Brazil), registration number: CEP 1147/11.

Context

Sixty female patients were selected from the rheumatology outpatient clinic of the UNIFESP between July 2011 and July 2012.The individuals were recruited consecutively and assigned to the painful or painless synovitis group. The monitoring and data collection period were: July 2011 to July 2013 and July 2013 to December 2015, respectively. All the patients gave their written informed consent.

Participants

Patients with a diagnosis of RA according to the classification criteria of the American College of Rheumatology (ACR) 1987 (15) were included in the study. Established disease was considered in patients with a diagnosis of RA for more than one year.

Patients had to have swelling in at least two metacarpophalangeal joints (MCPs) of both hands. Each joint needed to be painless in the "painless group" and painful in the "painful group" for at least six consecutive months with stable treatment during the last three months. The pain criterion was a visual analogue scale (VAS) of at least 4 cm in the MCP Painful group and 0 cm in the MCP Painless group (VAS range, 0–10 cm). Other joints were not assessed for the inclusion criteria.

Outcomes

The ultrasound bone erosion was our primary outcome, but inflammatory ultrasound measurements were also

assessed (T0 and T12 month). Secondary outcomes were (T0, T6 month and T12 month): demographic data and life habits, physical examination, morning stiffness, grip and pinch strength, hand function, quality of life, disease activity and radiographic findings. At T6 and T12, variables of clinical progression of disease, change of systemic (synthetic and biological) and local (intra-articular injections and surgery) treatment and rehabilitation were also assessed. The presence of new joint deformities (joint subluxation) in a categorical way (T0 and T12 months) was also evaluated but not evaluating the degree of each deformity.

Assessment

The US assessment was performed initially (T0) and at 12 months (T12) by a blinded radiologist who specialised in musculoskeletal radiology and had five years of experience in joint ultrasonography. The device used was a MyLab 60 Xvision (Esaote, Biomédica, Genova, Italy) with a linear transducer with a frequency range of 6–18 MHz; the examination followed the European League Against Rheumatism (EULAR) musculoskeletal US guidelines (16). The radiocarpal (RC), distal radioulnar (DRU) (dorsal surface), and first to fifth metacarpophalangeal (I-V MCP) joints (dorsal and volar surfaces) were assessed bilaterally according to the US parameters defined by Outcome Measures in Rheumatology (OMERACT) (17). In the semi-quantitative analyses of bone erosion, PD and SH, were used with the following scores: scores 0 and 1 for SH and bone erosion were considered normal, and scores 2 or 3 were pathological; score 0 for PD was normal and scores 1, 2 or 3 were considered pathological (24). Quantitative synovitis measurements were taken in the largest synovial recess of the joint between the joint capsule and the subchondral bone (18, 19).

The interobserver reproducibility of the ultrasonographic evaluation was assessed based on the evaluation of the images captured and recorded in 20% of the sample by a blinded rheumatologist trained in musculoskeletal ultrasonography.

Table I. Present characteristics of groups.

	Painless group (n=30)	Painful group (n=30)	*p*
Age (in years), mean ± SD	59.9 ± 11.5	56.8 ± 14.0	0.441*
Skin colour, n (%)			
White/Brown/Black	16(55)/10(35)/3(10)	11(41)/11(41)/5(18)	0.496**
Smoking, n (%)	2 (7)	9 (30)	0.042***
Alcohol use, n (%)	0 (0)	1 (3)	0.500***
Dominant right hand, n (%)	28 (93)	27 (90)	1.000***
Arterial hypertension, n (%)	15 (50)	23 (77)	0.032**
Dyslipidaemia, n (%)	8 27)	15 (50)	0.063**
Duration of disease (years) mean ± SD	17.7 ± 9.4	15.1 ± 10.2	0.185 ∞
T disease >5 years, n (%)	28 (93)	27 (90)	0.105***
Initial disease age, mean ± SD	41.4 ± 13.5	41.7 ± 14.2	0.948*
Duration of the absence or presence of MCPs pain (months), mean ± SD	30.3 ± 32.6	50.9 ± 74.6	0.740∞
Rheumatoid factor positive, n (%)	13 (43)	13 (43)	1.000**
Rheumatoid factor titre, mean ± SD	151.4 (264.0)	107.9 (181.2)	0.598∞
Anti-CCP positive, n (%)	23 (77)	19 (63)	0.098**
Use of MTX, n (%)	17 (57)	20 (67)	0.427**
Use of Leflunomide, n (%)	18 (60)	13 (43)	0.196**
Use of HDC, n (%)	1 (3)	4 (13)	0.353***
Use of CS via oral, n (%)	11 (37)	16 (53)	0.194**
Use of immunobiological agent, n (%)	5 (17)	11 (37)	0.080**
DMARD association, n (%)	9 (30)	11 (37)	0.584**
Immunobiological agent after 1 year of disease, n (%)	7 (23)	14 (48)	0.045**
ESR, mean ± SD	31.7 ± 21.8	31.5 ± 25.9	0.498∞
CRP (mg/dl), mean±SD	0.7 ± 1.0	0.7 ± 0.7	0.398∞
Functional status 1/ 2/ 3 n (%)	17(57)/ 10(35)/ 2(7)	11(37) /19(63) / 0 (0)	0.048**

SD: standard deviation; NS: non-statistical; *Student's t-test; **chi-square test; ∞ Mann-Whitney test; ***Fisher's exact test; OP: osteoporosis; MCPs: metacarpophalangeal joints; T: time; Anti-CCP: anti-cyclic citrullinated peptide; n: number; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate (mm/h); mg: milligrams; CS: corticosteroid (mg); MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs; DMARD association: 2 or more.

The clinical assessment was performed by a blinded rheumatologist initially (T0), at six months (T6), and at 12 months (T12). The clinical assessment consisted of physical examination, morning stiffness, grip and pinch strength, Cochin Hand Functional Scale (CHFS) (20), simplified HAQ questionnaire (21), DAS28 (22), SDAI (23), and CDAI (24).

Radiographic assessment was performed at T0 and T12 with a plain x-ray of the hands and wrists. The images were assessed at the end of the study by a single blinded radiologist according to the modified van der Heijde method (25).

During the 12-month follow-up, the patients were followed at UNIFESP and treated according to the RA treatment guidelines. Therapeutic interventions were not part of this study.

To avoid assessment bias, the number of painful joints was measured at the end of the physical examination.

Sample size

The sample size of 30 individuals in each group was considered appropriate, as the PD was the primary outcome of the study. PD was chosen because it better reflects US activity in RA disease than the other US variables, and because it is the most important ultrasound variable predicting joint damage in RA patients. The study used a standard deviation of 0.4, a power of 90%, and 5% significance level.

Statistical analysis

For the statistical analysis, repeated measures ANOVA of continuous or categorical variables was used (26). Student's t- or Mann-Whitney U-test, Chi-square test, or Fisher's exact test was performed for the initial comparison between groups. The inter-class correlation coefficient and Cohen's kappa coefficient (κ) were used to assess interobserver reproducibility. Significance was considered at 5%.

Results

Participants

230 patients were recruited initially to this study as potentially eligible; 28 were excluded because they did not have the availability of time and 12 refused to participate. 190 patients were examined for eligibility, but only 60 fitted the criteria with swelling and pain or without pain in MCPs joints mainly. Sixty patients were included in the study and they all completed the follow-up.

Initial demographic and general data

Sixty-six women with RA were studied. The patients had a mean age of 58.0±12.8 years and mean disease duration of 16.4±9.8 years. In our sample the clinical state of wrist pain and swelling coincided with that of MCPs in each group. Clinical and ultrasonographic assessments were performed in both hands of each patient, for a total of 120 hands, 600 MCPs, and 1560 joint recesses analysed at both T0 and T12. Therefore, by adding the joint recesses assessed ultrasonographically at T0 and T12, we evaluated a total of 3120 recesses.

Initially, the groups were similar in terms of their general and demographic characteristics, except for the presence of smoking and hypertension, which were more frequent in the Painful group (Table I). Disease activity scores and hand functional tests had worse indexes in the Painful group at T0 (0.001<ps<0.039) except for handgrip strength (p=0.289).

Ultrasound variables

There were no significant differences in the groups' evolution for the majority of the ultrasound measurements at the time points studied (Table II). For the bone erosion measurement, there was no difference between groups except for the distal radioulnar (DRU) recess (intergroup p=0.017) with worsening of this score in the Painful group (p=0.001).

Differences were found between groups in the following recesses: quantitative synovitis in the IV MCP volar recess and V MCP dorsal recess (ps<0.014), with an improvement of this score in the Painless group (p<0.001); semi-quantitative synovitis in the II MCP dorsal recess (p=0.013).

Over the one year, we found intragroup improvement in several scores evaluated (synovitis and PD), but this improvement occurred in both groups at most time points (ps<0.018). Conversely, the erosion score showed intragroup worsening over time, with an increase in the number of erosions and significant differences in a few recesses, such as the DRU in the Painful group and the I and III volar MCP in both groups (ps<0.018) (Table II). In some of the joint recesses studied, a slight erosion percentage improvement was observed, such as in the I, III, IV dorsal MCP, and IV volar MCP in the Painless group and II dorsal MCP in the Painful group (0.865<ps>0.216).

Moderate-to-strong interobserver reproducibility (κ=0.435-1, p<0.018) was observed for all of the evaluated recesses, and strong reproducibility was observed for the PD (κ=0.655-0.783; p=0.001).

Evolution data

We evaluated 60 patients at T0, 48 (80%) patients at T6 and 60 patients at T12. The sample at T6 included 28 female patients in the Painful group and 20 in the Painless group. At T6, the sample was assessed clinically. Among these patients, 5 (18%) in the Painful group stopped having pain in the MCPs, whereas 3 (15%) patients in the Painless group started to experience joint pain.

The initial 60 patients also underwent clinical, laboratory and US assessments at T12. At this time point, 5 (17%) patients in the Painful group stopped having pain relative to T0, and 2 (7%) from the Painless group started having pain in the MCPs (p=0.424). Regardless of this change in symptomology at T6 and T12, all patients continued to be assessed in their source groups.

Disease activity indices

In the disease activity score evaluations, the patients of the Painful group presented worse scores only in DAS28 (p<0.042). The Painful group presented an improved DAS28-ESR at T12 relative to T0 (p<0.001), whereas the Painless group showed a worsened DAS28-CRP at T6 and improvement at T12 (p<0.007). Both groups had an improvement in the number of swollen joints, and SDAI and CDAI scores over the one year (intragroup ps<0.002) (Table III).

Functional tests/strength

The Painful group also presented worse scores for some of the strength tests (lateral, pulp-to-pulp, and tripod pinch) (ps<0.014). In the intragroup evaluation, both groups showed worse strength in the grip strength test (ps<0.001). The Painless group patients improved in the pulp-to-pulp and tripod pinch strength (ps<0.002), whereas those in the Painful group showed a worsening of the lateral pinch (p<0.012) at one year (T12) with respect to the baseline (T0) (Table IV).

Clinical/treatment variables

The groups progressed in a similarly statistic way (ps>0.05) in the following variables: new joints deformities, systemic or intraarticular pharmacological treatment change, and indication of other therapeutic interventions assessed at T6 and T12. In the intragroup evaluation, a significant difference was found in the need for combination with a new disease-modifying drug in both groups (ps<0.001). Only one patient belonging to the Painful group underwent joint surgery in the MCP during the study period (Table V).

Radiographic variables

The modified Sharp score for hands, which had a maximum final value of 280, was calculated to evaluate erosion using x-ray. The Painless and Painful groups had total scores of 88.5±57.2 and 64.8±41.1 at baseline and scores of 95.2±48.8 and 77.2±45.2 at 12 months, respectively. No significant differences were observed between the groups (p=0.100), although worsening of the score over the 1 year was observed in both groups (intragroup p=0.007). In a sub-analysis of the x-ray evaluation, we observed that the number of MCP erosions worsened over time in both groups (intragroup p<0.001, but intergroup p=0.404). The same phenomenon

Table II. Comparison of groups at one year regarding ultrasound findings per joint- synovial hypertrophy, PD and bone erosion.

	Quantitative SH (mm) mean ± SD			Semiquantitative SH scores >2 n (%)			Semiquantitative PD scores >1 n (%)			Semiquantitative erosion scores >2 n (%)		
Joint Recesses	Painless Group n=60	Painful Group n=60	Inter group *p*	Painless Group n=60	Painful Group n=60	Inter group *p*	Painless Group n=60	Painful Group n=60	Inter group *p*	Painless Group n=60	Painful Group n=60	Inter group *p*
RC												
T0	3.0 ± 2.0	2.8 ± 2.2	0.941⇊	22(37)	18 (30)	0.529¬	25 (42)	14 (23)	*0.066*¬	57 (95)	53 (88)	0.335¬
T12	2.1 ± 1.7	2.2 ± 2.0		16 (27)	14 (24)		10 (17)	8 (14)		57 (95)	55 (95)	
Intragroup ***p***	<0.001⇊	<0.001⇊		*0.051*¬	*0.051*¬		<0.001¬	<0.001¬		0.264¬	0.264¬	
DRU												
T0	3.3 ± 2.3	3.1 ± 2.1	*0.471*⇊	23 (38)	12 (20)	*0.066*¬	25 (42)	16 (27)	0.954¬	56 (95)	46 (77)	0.017¬
T12	3.0 ± 2.7	2.7 ± 2.3		21 (35)	16 (28)		19 (32)	10 (17)		58 (97)	57 (95)	
Intragroup ***p***	*0.193*⇊	*0.193*⇊		*0.646*¬	*0.646*¬		*0.051*¬	0.051¬		*0.547*¬	0.001¬	
I MCP												
Dorsal- T0	1.6 ± 1.7	1.2 ± 1.5	*0.659*⇊	16 (27)	15 (25)	0.965¬	13 (22)	12 (20)	*0.733*¬	47 (78)	40 (67)	0.462¬
T12	1.3 ± 1.4	1.4 ± 1.9		16 (27)	17 (30)		13 (22)	10 (17)		46 (77)	44 (77)	
Intragroup ***p***	*0.568*⇊	*0.568*⇊		*0.630*¬	*0.630*¬		*0.625*¬	*0.625*¬		*0.216*¬	0.216¬	
I MCP												
Volar- T0	1.6 ± 1.6	1,3 ± 1,6	*0.177*⇊	36 (60)	29 (38)	0.115¬	15 (25)	8 (13)	*0.385*¬	51 (85)	42 (70)	0.027¬
T12	0.9 ± 1.4	0,6 ± 1,2		10 (17)	6 (11)		3 (5)	5 (9)		57 (95)	51 (90)	
Intragroup ***p***	<0.001⇊	<0.001⇊		0.011¬	0.011¬		*0.002*¬	*0.002*¬		0.001¬	0.001¬	
II MCP												
Dorsal- T0	2.6 ± 2.1	2.3 ± 1.8	*0.723*⇊	34 (57)	24 (40)	0.013¬	27 (45)	17 (28)	*0.177*¬	54 (90)	51 (85)	0.235¬
T12	2.2 ± 1.9	2.3 ± 2.3		32 (53)	19(33)		19 (32)	18 (31)		55 (92)	50 (86)	
Intragroup ***p***	*0.280*⇊	0.280⇊		*0.293*¬	*0.293*¬		*0.398*¬	*0.398*¬		0.718¬	0.718¬	
II MCP												
Volar - T0	2.2 ± 2.0	1.8 ± 1.9	*0.436*⇊	27 (45)	19 (32)	*0.269*¬	13 (22)	11 (18)	*0.722*¬	53 (88)	44 (73)	0.089¬
T12	1.5 ± 1.7	1.5 ± 1.9		17 (28)	15 (26)		4 (7)	8 (14)		53 (88)	48 (83)	
Intragroup ***p***	0.001⇊	0.001⇊		0.017¬	0.017¬		0.009¬	0.009¬		0.314¬	*0.314*¬	
II MCP												
Lateral -T0										57 (95)	44 (75)	0.098¬
T12										57 (95)	48 (86)	
Intragroup ***p***										0.098¬	0.098¬	
III MCP												
Dorsal- T0	1.9 ± 1.8	1.8 ± 1.7	*0.905*⇊	21 (35)	18 (30)	*0.767*¬	16 (27)	14 (23)	*0.855*¬	51 (85)	43 (72)	0.481¬
T12	1.5 ± 1.6	1.8 ± 2.1		13(22)	18 (31)		15 (25)	15 (26)		45 (75)	46 (80)	
Intragroup ***p***	*0.200*⇊	*0.200*⇊		*0.122*¬	*0.122*¬		*0.919*¬	*0.919*¬		0.776¬	0.776¬	
III MCP												
Volar - T0	1.5 ± 1.7	1.3 ± 1.7	*0.858*⇊	20 (33)	15 (25)	*0.525*¬	9 (15)	8 (13)	*0.831*¬	42 (70)	42 (70)	0.857¬
T12	0.7 ± 1.2	0.8 ± 1.6		8 (13)	8 (14)		1 (2)	1 (2)		49 (82)	46 (79)	
Intragroup ***p***	<0.001⇊	<0.001⇊		<0.001¬	<0.001¬		<0.001¬	<0.001¬		0.018¬	0.018¬	
IV MCP												
Dorsal - T0	1.4 ± 1.7	1.3 ± 1.7	*0.568*⇊	12(20)	11 (18)	*0.659*¬	9 (15)	10 (17)	*0.389*¬	33 (55)	28 (47)	0.463¬
T12	1.1 ± 1.6	0.6 ± 1.3		8 (13)	12 (21)		6 (10)	10 (17)		32 (53)	29 (50)	
Intragroup ***p***	*0.727*⇊	*0.727*⇊		*0.466*¬	*0.466*¬		0.580¬	*0.580*¬		0.858¬	0.858¬	
IV MCP												
Volar - T0	1.3 ± 1.7	0.8 ± 1.2	*0.004*⇊	14 (23)	9 (15)	*0.449*¬	3 (5)	3 (5)	*0.295*¬	34 (58)	29 (50)	0.666¬
T12	0.6 ± 1,3	0.9 ± 1.5		11 (18)	10 (17)		0 (0)	3 (5)		32 (53)	32 (55)	
Intragroup ***p***	<0,001⇊	*0.775*⇊		*0.694*¬	*0.694*¬		*0.324*¬	*0.342*¬		0.865¬	0.865¬	
V MCP												
Dorsal - T0	2.1 ± 2.0	1.8 ± 2.1	*0.014*⇊	23 (38)	19 (32)	*0.854*¬	11 (18)	11 (18)	*0.690*¬	56 (93)	48 (80)	*0.299*¬
T12	1.0 ± 1.5	1.6 ± 2.1		10 (17)	12 (21)		4 (7)	6 (10)		51 (85)	51 (88)	
Intragroup ***p***	<0.001⇊	*0.624*⇊		*<0.001*¬	*<0.001*¬		0.018¬	0.018¬		0.956¬	0.956¬	
V MCP												
Volar - T0	1.4 ± 2.2	1.1 ± 1.6	0.582⇊	14 (23)	13 (22)	0.197¬	6 (10	6 (10)	0.592¬	33 (55)	22 (37)	0.077¬
T12	0.4 ± 0.9	0.5 ± 1.0		6 (10)	7 (12)		0 (0)	2 (3)		35 (58)	29 (50)	
Intragroup *p*	<0.001⇊	<0.001⇊		*<0.001*¬	*<0.001*¬		0.003¬	0.003¬		*0.139*¬	0.139¬	

SD: standard deviation; JR: joint recesses; RC: radiocarpal; DRU: distal radioulnar; P: palmar; D: dorsal; L: lateral; MCP: metacarpophalangeal; ⇊ repeated measures numerical ANOVA; ¬ repeated measures categorical ANOVA.

Table III. Comparison of groups at one year regarding activity index scores.

	Painless group (n=30) Mean ± SD	Painful group (n=30) Mean ± SD	Intergroup *p*
Morning stiffness			
T0	5.3 ± 15.8	21.3 ± 24.0	<0.001*
T6	1.2 ± 4.8	20.0 ± 3.5	0.763***
T12	4.1 ± 14.6	15.5 ± 37.7	
Intragroup *p* ⇓	0.772	0.772	
MDGA			
T0	32.1 ± 17.5	50.4 ± 15.7	<0.001*
T6	31.0 ± 18.2	47.0 ± 19.9	0.101***
T12	24.2 ± 21.2	54.2 ± 16.4	
Intragroup *p*⇓	0.760	0.760	
PGA			
T0	29.0 ± 26.7	58.6 ± 19.2	<0.001*
T6	34.0 ± 25.4	52.1 ± 24.0	0.200***
T12	26.0 ± 26.2	56.4 ± 21.1	
Intragroup *p* ⇓	0.783	0.783	
N painful joints			
T0	1.7 ± 2.6	13.0 ± 5.6	<0.001*
T6	7.5 ± 8.6	12.9 ± 8.5	0.084***
T12	2.9 ± 4.2	11.2 ± 9.1	
Intragroup *p* ⇓	>0.100	>0.100	
N swollen joints			
T0	8.1 ± 2.8	9.7 ± 3.8	0.246*
T6	6.4 ± 4.4	8.0 ± 5.4	0.787***
T12	2.3 ± 2.3	4.8 ± 4.5	
Intragroup *p* ⇓	<0.001	<0.001	
DAS 28 by ESR			
T0	3.6 ± 0.9	5.5 ± 1.0	<0.001**
T6	4.4 ± 1.5	5.0 ± 1.2	0.022***
T12	3.1 ± 1.4	4.45 ± 1.0	
Intragroup *p* ⇓	>0.133	<0.001	
DAS 28 by CRP (mg/L)			
T0	3.0 ± 0.9	4.8 ± 1.0	<0.001**
T6	4.0 ± 1.5	4.8 ± 0.9	0.042***
T12	2.6 ± 0.9	4.1 ± 1.0	
Intragroup *p* ⇓	0.007	0.016	
SDAI			
T0	15.0 ± 7.5	29.4 ± 10.3	<0.001**
T6	20.7 ± 14.6	27.0 ± 11.7	0.089***
T12	8.8 ± 6.0	23.0 ± 9.6	
Intragroup *p* ⇓	0.001	0.001	
CDAI			
T0	15.1 ± 6.9	28.4 ± 9.1	<0.001**
T6	17.6 ± 11.7	26.1 ± 11.4	0.219***
T12	9.5 ± 7.4	23.5 ± 9.9	
Intragroup *p* ⇓	0.002	0.002	

SD: standard deviation; MDGA: physician's global assessment; PGA: patient's global assessment; n: number; DAS-28: 28-Joint Disease Activity Score; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate (mm/h); NS: non-statistical; ⇓repeated measures ANOVA; *p intergroup no T0, Mann-Whitney test; **p intergroup no T0, Student's t test; *** p intergroup T0-T12, repeated measures ANOVA.

was observed with the MCP joint space, which decreased at one year without significant intra- and intergroup differences (sp=0.295 and p=0.737, respectively).

Discussion

In this one-year cohort, we observed a very similar evolution between the Painless and Painful groups for the ultrasound bone erosion and the majority of the assessment tools. This group was the first to study these RA patients and persistent painless joint swelling in a controlled study, which we called "painless synovitis" (14).

This article has some limitations. The main one is that the study enrolled only women, with features suggesting the inclusion of a population of longstanding RA with features of disabling disease that does not reflect the condition of the majority of current RA patients. Another limitation was the difficulty in capturing individuals for the two analysed groups who maintained the same pain status (presence or absence of pain) exactly in an equal number of swollen joints at T0 and during the whole follow-up time. However, this finding reinforces the impression that pain may change under the influence of several factors, including non-inflammatory factors, and that we should give greater importance to persistent joint swelling. Another point is that clinical activity in other joints in the different groups could influence some results. The wrist US tried to find another inflammation site close to the MCPs studied. Another limitation was not having performed intra-reader US reproducibility.

The most important finding of this study was that the two groups evolved in a very similar way regarding the ultrasound measurement of bone erosion. This suggests that pain does not influence the progression of bone damage in women with established RA. In this study, we also observed a slight improvement in the percentage of bone erosions in some joint recesses studied (ps>0.216), which is also reported in the current literature (27-29). This curious finding was more frequent in the Painless group. This outcome warrants investigation because it challenges the understanding of the pathophysiology of RA. However, as discussed earlier, although US evaluation has good reproducibility if performed by a trained professional, this method is a subjective measure and this may explain the improvement of the erosion percentage in this study. Another factor that may have contributed to this finding is the improvement in the synovitis scores in

Table IV. Comparison of groups at one year regarding functional assessment.

	Painless group (n=30) Mean ± SD	Painful group (n=30) Mean ± SD	Intergroup *p*
HAQ			
T0	0.4 ± 0.4	1.1 ± 0.6	<0.001*
T6	0.4 ± 0.3	0.9 ± 0.4	0.485***
T12	0.3 ± 0.3	0.8 ± 0.4	
Intragroup *p* ⇓	0.060	0.060	
Cochin			
T0	8.9 ± 11.4	24.8 ± 16.0	<0.001*
T6	6.0 ± 5.4	20.8 ± 12.4	0.920***
T12	5.1 ± 6.1	20.0 ± 13.9	
Intragroup *p* ⇓	>0.116	>0.116	
Jamar			
T0	21.2 ± 13.0	19.7 ± 14.7	0.284*
T6	13.0 ± 7.5	10.1 ± 6.2	0.250***
T12	14.2 ± 6.8	9.3 ± 6.1	
Intragroup *p* ⇓	<0.001	<0.001	
Lateral pinch			
T0	4.8 ± 1.5	3.8 ± 1.7	<0.001*
T6	4.6 ± 1.4	3.5 ± 1.6	0.014***
T12	5.0 ± 1.5	3.3 ± 1.3	
Intragroup *p* ⇓	0.129	0.012	
Pulp-to-pulp pinch			
T0	3.1 ± 1.3	2.7 ± 1.3	0.069*
T6	3.9 ± 1.5	2.8 ± 1.3	0.001***
T12	4.0 ± 1.7	2.7 ± 1.3	
Intragroup *p* ⇓	<0.001	0.530	
Tripod pinch			
T0	3.5 ± 1.3	3.2 ± 1.6	0.039*
T6	3.9 ± 1.5	3.0 ± 1.4	0.003***
T12	4.2 ± 1.7	3.0 ± 1.4	
Intragroup *p* ⇓	0.002	0.401	

SD: standard deviation; HAQ: simplified Stanford Health Assessment Questionnaire[25]; Jamar: grip strength with Jamar dynamometer (Ansinow Engineering Co); Lateral, pulp-pulp and tripod pinch: pinch strength with the Preston Gauge dynamometer (B&L Engeneering Co); NS: non-statistical; ⇓repeated measures ANOVA; **p* intergroup no T0, Mann-whitney test; ****p* intergroup T0-T12, repeated measures ANOVA.

both groups, which may influence the study of bone erosion.

The majority of our studied patients had a longstanding RA diagnosis (17.7±9.4 and 15.1±10.2 years in the Painless and Painful, respectively), which characterised late RA (30). A painless joint swelling is often observed by healthcare professionals in these patients, which they refer to as "fibrous synovitis", "cold synovitis", or is even referred to in the literature as "boggy joints" (joints that feel "boggy" and enlarged on palpation) (31-34).

However, according to Felson *et al*. (30), joint swollen is the true predictor of late radiographic progression. Bugatti *et al*. (35) also reported that the progression of radiographic joint damage in individuals considered to be in remission might be related to residual joint swelling.

In a few patients in this study, the painful and painless symptomatology was not a continuous feature from the beginning to the end of follow-up. The perception of pain is highly subjective and can be influenced by several aspects, including socio-cultural factors (18, 19).

However, pain control is a priority for 90% of RA patients, although several studies have shown that pain in this disease may be related to factors other than joint inflammation (7-8, 36-39) The intense, persistent, or refractory inflammatory activity in these patients leads to joint destruction and may be a determinant of more severe RA radiographic progression (35).

In this study, both groups presented active disease according to the swollen joint counts and SDAI as proposed by the ACR/EULAR (40), with the lowest disease activity rates (DAS28, SDAI, and CDAI; $p<0.001$) in the Painless group at baseline. In the longitudinal evaluation at baseline, T6, and T12, the Painful group had worse activity indices only in the DAS28 ($p<0.042$). Additionally, some indices showed improvement over the one year in both groups ($p<0.002$), which could suggest that there was an attempt by medical professionals to control the disease in both groups.

In the functional evaluation, the Painful group had a worse strength test ($ps<0.014$), and no difference between the groups was found in the functional questionnaires over the 1-year period. The HAQ and Cochin tests are based on questions with subjective responses by the patients (25, 26) that can be influenced by the pain symptoms. In contrast, the grip and pinch strength tests (Jamar® and Preston Pinch Gauge® dynamometers) are objective measures, but they can also be influenced by joint pain, weight, height, age of the patient, and test application time (41). In this study, we observed that Painless group patients evolved with improvement in some of the strength tests ($ps<0.002$), whereas Painful group patients evolved with worsening in other tests ($ps<0.012$). These findings support the hypothesis that pain can influence these tests.

Evidence in the literature indicates that progression of joint damage occurs in RA despite clinical remission (42). Special attention has been paid to the ability of US to detect subclinical synovitis and to predict future structural damage (12), with PD serving as a tool to aid in the detection of 'active' synovitis (43, 44). An intriguing question is why many rheumatologists ignore the relevance of persistent joint swelling when it is painless despite evidence that subclinical synovitis predicts future joint damage.

Table V. Comparison of groups at one year regarding treatment change, clinical data and other therapeutic interventions.

	Painless group (n=30) n (%)	Painful group (n=30) n (%)	Intergroup *p*
Treatment change			
T6	6 (35)	11 (42)	0.844¬
T12	7 (41)	9 (35)	
Intragroup *p* ¬	0.925	0.925	
New DMARD association			
T6	7 (41)	17 (63)	0.413¬
T12	5 (29)	8 (30)	
Intragroup *p* ¬	<0,001	<0,001	
DMARD change			
T6	1 (6)	0 (0)	0.687¬
T12	1 (6)	2 (7)	
Intragroup *p* ¬	0.439	0.439	
New biological agent use			
T6	2 (10)	2 (7)	0.867¬
T12	1 (5)	3 (11)	
Intragroup *p* ¬	0.879	0.879	
Biological agent change			
T6	1 (5)	0 (0)	0.531¬
T12	1 (5)	1 (4)	
Intragroup *p* ¬	0.317	0.317	
Continuous oral CS use			
T6	7 (44)	14 (54)	0.541¬
T12	8 (50)	12 (46)	
Intragroup *p*	0.296	0.296	
Cumulative oral CS use (mg)-mean ± SD			
T6	455,3 ± 645,4	592,9 ± 819,4	0.911 ⇓
T12	745,3 ± 1016,8	663,6 ± 1140,9	
Intragroup *p* ⇓	0.294	0.294	
N° of CS IAI: MCP/ wrist/others			
T6	1(6)/ 1(6)/ 2(12)	2(8)/ 1(4)/ 0(0)	0.355¬
T12	1(6)/ 2(12)/ 1(6)	1(4)/ 0(0)/ 2(8)	
Intragroup *p* ¬	0.997	0.997	
New deformity MCPs/foot/ others			
T6	1(6)/ 1(6)/ 1(6)	4(14)/ 3(11)/ 1(4)	0.138¬
T12	2(12)/ 0(0)/ 1(6)	5(18)/ 2(7)/ 3(11)	
Intragroup *p* ¬	0.782	0.782	
Start rehabilitation			
T6	3 (16)	1 (4)	0.115¬
T12	5 (26)	3 (11)	
Intragroup *p* ¬	0.163	0.163	
Start using hand orthosis			
T6	2 (10)	1 (4)	0.710¬
T12	2 (11)	0 (0)	
Intragroup *p* ¬	0.919	0.919	

SD: standard deviation; CS: corticosteroid; T: time; n: number; IAI: intra-articular injection; DMARDs: disease-modifying anti-rheumatic drugs; DMARD association: 2 or more; MCPs: metacarpophalangeal joints; ∞ Mann-Whitney test; NS: non-statistical; ⇓repeated measures ANOVA; ¬ repeated measures categorical ANOVA.

An important contribution of the present study is the attempt to differentiate the evolution of the two studied groups, especially regarding the US findings. An investigation of whether the absence of pain in RA synovitis is associated with better evolution of the joint US scores was also investigated, especially regarding the detection of bone erosion. Both groups evolved in a very similar manner or still presented worse scores in the Painless group at T0, such as DRU bone erosion (p<0.017). The chronic disease in the patients studied may have influenced the low positive PD percentage in both groups and the high erosion prevalence. These characteristics may have affected the evolution of the longitudinal groups.

The similarities shown between the Painful and Painless group evolution for both the semi-quantitative and quantitative US variables in MCPs may suggest that painless synovitis is not free of risk of RA progression and may result in disabilities. Data related to the findings of this study are not found in the literature.

PD positivity is associated with inflammatory process activity, a predictor of damage and disease relapse (45, 46). Therefore we chose PD to calculate the size of our sample. However, PD is a tool that depends on the quality of the US device, the force applied to the probe by the examiner, the patient's position, the weather conditions, and the time of the test (46, 47). In the study by Brown *et al*. (42), the PD signal positive in patients with RA in remission was associated with the progression of joint damage. In this study, a minority of patients had a positive PD, which could be explained by the chronicity of the patients studied or explain the non-significant evolution of the erosion score in both groups.

X-ray is still the most common imaging method used in clinical trials to evaluate RA joint damage, and the van der Heijde-modified Sharp score is the most commonly used score in clinical trials (48, 49). In this study, the Sharp score showed similar structural changes between the groups (p=0.100), although there was worsening of the scores over the 1-year period in both groups. The prolonged disease duration of the studied patients might have led to a poor radiographic score from the beginning of the study.

We know that findings only in women and with long-standing RA cannot be

generalised. However, the subgroup of patients with painless synovitis exists and studies such as ours suggest less importance of pain in the evolution of joint damage in these patients.

The management of RA with its clinical and subclinical heterogeneity of presentation remains a challenge for the rheumatologist. RA patients with chronic painless joint swelling increasingly intrigue researchers of this disease. The significance of this painless synovitis is uncertain. Thus, the clinical and radiological characteristics of this type of synovitis compared to painful synovitis should be better characterised.

Conclusion

According to the results of the present study, we can conclude that female patients with established RA with pain evolve similarly to patients who have painless joint swollen. More controlled and prospective studies are needed to test these findings and to study the real importance of painless synovitis in these patients.

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References

1. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid Arthritis Classification Criteria. Arthritis Rheum 2010; 62: 2569-81.
2. GASTON JS: Cellular immunity in rheumatoid arthritis. *In*: HOCHBERG MC, SILMAN AJ, SMOLEN JS *et al*.: Rheumatology. Fourth edition. Elsevier; 2007, p. 829-35.
3. GRASSI W, ANGELIS RD, LAMANNA G *et al*.: The clinical features of rheumatoid arthritis. *Eur J Radiol* 1998; 27: S18-S24.
4. SHERRY DD, BOHNSACK J, SALMONSON K *et al*.: Painless juvenile rheumatoid arthritis. *J Pediatr* 1990; 116: 921-23.
5. LAAKSONEN LA, LAINE V: A comparative study of joint pain in adult and juvenile rheumatoid arthritis. *Ann Rheum Dis* 1961; 20: 386.
6. HORSTEN NCA, URSUM J, ROORDA LD *et al*.: Prevalence of hand symptoms, impairments and activity limitations in rheumatoid arthritis in relation to disease duration. *J Rehabil Med* 2010; 42: 916-21.
7. WALSH DA, MCWILLIAMS DF: Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol* 2014; 10: 581-92.
8. RIFBJERG-MADSEN S, CHRISTENSEN AW, BOESEN M *et al*.: Can the pain DETECTED Questionnarie score and MRI help predict treatment outcome in rheumatoid arthritis: protocol for the Frederiksberg hospital's Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME-Cohort) study. *BMJ Open* 2014; 4: e005068.
9. NAREDO E, IAGNOCCO A: One year in review: ultrasound in arthritis. *Clin Exp Rheumatol* 2016; 34: 1-10.
10. BROWN AK, QUINN MA, KARIM Z *et al*.: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission – Evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761-73.
11. SZKUDLAREK M, TERSLEV L, WAKEFIELD RJ *et al*.: Summary findings of a systematic literature review of the ultrasound assessment of bone erosions in rheumatoid arthritis. *J Rheumatol* 2016; 43: 12-21.
12. DOUGADOS M, DEVAUCHELLE-PENSEC V, FERLET FJ *et al*.: The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. *Ann Rheum Dis* 2013; 72: 665-71.
13. D'AGOSTINO MA, TERSLEV L, WAKEFIELD R *et al*.: Novel Algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. *Ann Rheum Dis* 2016; 75: 1902-8.
14. PEREIRA DF, NATOUR J, BUOSI AL *et al*.: Is painless synovitis different from painful synovitis? a controlled, ultrasound, radiographic, clinical trial. *Clinics* (Sao Paolo) 2014; 69: 93-100.
15. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
16. BACKHAUS M, BURMESTER G-R, GERBER T *et al*.: Guidelines for musculoskeletal ultrasound in Rheumatology. *Ann Rheum Dis* 2001; 60: 641-9.
17. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Proceedings from the OMERACT Special Interest Group for Musculoskeletal Ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
18. SCHMIDT WA, SCHMIDT H, SCHICKE B *et al*.: Standard reference values for musculo skeletal ultrasonography. *Ann Rheum Dis* 2004; 63: 988-94.
19. SZKUDLAREK M, COURT-PAYEN M, JACOBSEN S *et al*.: Interobserver agreement in ultrassonography of the finger and toe joint in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 955-62.
20. CHIARI A, SARDIM CCS, NATOUR J: Translation, cultural adaptation and reproducibility ot the Cochin Hand Functional Scale questionnaire for Brazil. *Clinics* (Sao Paolo) 2011; 66: 731-6.
21. FERRAZ MB, LIVEIRA LM, ARAUJO PM *et al*.: EPM-ROM Scale: na evaluative instrument to be used in rheumatoid arthritis trials. *Clin Exp Rheumatol* 1990; 8: 491-4.
22. PREVOO MLL, VAN'T HOF MA, KUPER HH *et al*.: Modified disease activity scores that include twenty-eight-joint counts – Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 30: 44-8.
23. SMOLEN JS, BREEDVELD FC, SCHIFF MH *et al*.: A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 2003; 42: 244-57.
24. ALETAHA D, SMOLEN J: The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23 (Suppl. 39): S100-8
25. VAN DER HEIJDE DM: Plain x-rays in rheumatoid arthritis: overview of scoring methods, their rehability and applicability. *Baillieres Clin Rheumatol* 1996; 10: 435-53.
26. BRUNNER E, LANGER F: Nonparametric analysis of ordered categorical data in designs with longitudinal observations and small sample sizes. *Biometrical Journal* 2000; 42: 663-75.
27. DØHN UM, EJBJERG B, BOONEN A *et al*.: No overall progression and occasional repair of erosion despite persistent inflammation in rheumatoid adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrassonography, CT and radiography study. *Ann Rheum Dis* 2011; 70: 252-8.
28. DØHN UM, BOONEN A, HETLAND ML *et al*.: Erosive progression is minimal, but erosion healing rare, in patients with rheumatoid arthritis treated with adalimumab. A 1-year investigator-initiated follow-up study using high-resolution computed tomography as the primary outcome measure. *Ann Rheum Dis* 2009; 68: 1585-90.
29. LUKAS C, VAN DER HEIJDE D, FATENAJAD SAEED *et al*.: Repair of erosions occurs almost exclusively in damaged joints without swelling. *Ann Rheum Dis* 2010; 69: 851-55.
30. FELSON D: Defining remission in rheumatoid arthritis. *Ann Rheum Dis* 2012; 71 (Supp II): i86-i88.
31. ALTMAN RD, GRAY R: Diagnostic and therapeutic uses of the arthroscope in rheumatoid arthritis and osteoarthritis. *Am J Med* 1983; 75: 50-5.
32. O'BRIEN ET: Surgical principles and planning for the rheumatoid hand and wrist. *Clin Plast Surg* 1996; 23: 407-20.
33. JABS DA, HOUK JL, BIAS WB *et al*.: Familial granulomatous synovitis, uveitis, and cranial neuropathies. *Am J Med* 1985; 78: 801-4.
34. KEYFES V, HALBRECHT J: Arthroscopic debridement of loose bodies from a popliteal cyst. *Orthopedics* 2010; 16: 269-71.
35. BUGATTI S, MANZO A, CAPORATI R *et al*.: Assessment of synovitis to predict bone erosions in rheumatoid arthritis. *Ther Adv Musculoskeletal Dis* 2012; 4: 235-44.
36. LEE YC, CUI J, LU BING *et al*.: Pain persist in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther* 2011; 13: R83.
37. ULUS Y, AKYOL Y, TANDER B *et al*.: Sleep quality in fibromyalgia and rheumatoid ar-

thritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S92-96.
38. COUVOISIER DS, AGORITSAS T, GLAUSER J *et al*.: Pain as an Important Predictor of Psychosocial Health in Patients with Rheumatoid Arthritis. *Arthritis Care Res* 2012; 64: 190-96.
39. BJORK M, TRUPIN L, THYBERG I *et al*.: Difference in activity limitation, pain intensity, and global health in patients with rheumatoid arthritis in Sweden and the USA: a 5-year follow-up. *Scand J Rheumatol* 2011; 40: 428-32.
40. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials. *Ann Rheum Dis* 2011; 70: 404-13.
41. FIGUEIREDO IM, SAMPAIO RF, MANCINI MC *et al*.: Teste de força de preensão utilizando o dinamômetro Jamar. *Acta Fisiatr* 2007; 14: 104-10.
42. BROWN AK, CONAGHAN, KARIM Z *et al*.: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008; 10: 2958-67.
43. NAREDO E, MOLLER I, CRUZ A *et al*.: Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2248-56.
44. ZABOTTI A, MANDL P, ZAMPOGNA G *et al*.: One year in review 2018: ultrasonography in rheumatoid arthritis and psoriatic arthritis. *Clin Exp Rheumatol* 2018; 36: 519-25.
45. NAREDO E, BONILLA G, GAMERO F *et al*.: Assessment of inflamatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with gray scale e power Doppler ultrasonography. *Ann Rheum Dis* 2005; 64: 375-81.
46. GRASSI W, FILIPPUCCI E: Ultrasonography and the rheumatologist. *Curr Opin Rheumatol* 2007; 19: 55-60
47. SEMERANO L, GUTIERREZ M, FALGARONE G *et al*.: Diurnal variation of power Doppler in metacarpophalangeal joints of patients with rheumatoid arthritis: a preliminary study. *Ann Rheum Dis* 2011; 70:1699-700.
48. LILLEGRAVEN S, VAN DER HEIJDE D, UHLIG T *et al*.: What is the clinical relevance of erosions and joint space narrowing in RA? *Nat Rev Rheumatol* 2012; 8: 117-20.
49. LANDEWÉ R, VAN DER HEIJDE D: Presentation and analysis of radiographic data in clinical trials and observational studies. *Ann Rheum Dis* 2005; 64: iv48–iv51.