European Journal of Radiology 118 (2019) 10–18

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Optimization of ultrasonographic examination for the diagnosis of erosive Rheumatoid Arthritis in comparison to erosive hand Osteoarthritis

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Osteoarthritis
Ultrasounds
Radiography
Erosion
Diagnostic score

ABSTRACT

Objective: to determine thresholds and better scenario for the diagnosis of erosive rheumatoid arthritis (RA) by ultrasonography (US) in RA in comparison to osteoarthritic (OA) patients.
Methods: Patients, prospectively included, fulfilling ACR 1987; ACR/EULAR 2010 criteria for RA or hand OA criteria. Radiographic assessment (RX): Sharp erosion score, evaluated by two blinded readers and one adjudicator for discordant cases (number of eroded joints ≤ three). Definition of eroded RX RA: EULAR 2013 Definition. In US, erosions were scored on six bilateral joints (MCP2-3, 5; MTP2-3, 5) with a four-grade scale.
Results: A total of 168 patients were included: 122 RA (32 early RA < 2 years; 90 late RA ≥ 2 years); 46 OA patients. On RX: 42 RA patients (6 early; 36 late) and 5 OA patients have erosive diseases (sensitivity: 34.4%, specificity: 89.1%). On US, 95 RA patients (21 early; 78 late) and 12 OA patients have erosive diseases. Considering at least two joint facets eroded (threshold 1) or at least one joint facet eroded at grade 2 (threshold 2), sensitivities were good (68 and 72.1%), specificities excellent (89.1 and 100%). With only six targeted joint facets examined (6/30), sensitivities and specificities remained good (59.8 and 60.0%) and excellent (95.6 and 100%) with threshold 1 and 2 respectively. For all scenarios, agreement between RX and US for erosive RA was excellent ranged from 88.1% to 92.8%.
Conclusion: US erosion assessment of six targeted joint facets detected 1.7 times more erosive RA patients than RX in late and early RA with good sensitivity and excellent specificity.

1. Introduction

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory joint disease [1,2] responsible for structural damage. To limit these consequences, an international consensus recommended a therapeutic strategy based on early diagnosis and search for poor prognostic factors in order to optimize the tight control of disease activity. [3] Erosions on radiographs (RX), high levels of biologic inflammation parameters, and the presence of anti-cyclic citrullinated peptide antibodies (ACPA) [4] are the main predictive factors of bone erosions on RX, which is considered the gold standard for visualizing and quantifying bone lesions in RA (erosions and joint space narrowing) [5]. The Van der Heijde-modified Sharp score [6] with its good intra- and inter-reader reliabilities and good sensitivity to change [7,8], is considered as the standard scoring method to assess structural damage in RA.

Musculoskeletal ultrasounds (US) is booming in clinical practice for the diagnosis and evaluation of inflammatory lesions from inflammatory disorders, and it has been proven to be effective in the evaluation of bone erosions in various musculoskeletal diseases: osteoarthritis (OA), [9,10] gout [11], and psoriatic arthritis (PsA) [12]. In RA, many studies have shown that US can detect more erosions than RX at the joint level, especially at an early stage of the disease, with higher sensitivity and specificity than RX when a CT scan is taken as the gold

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https://doi.org/10.1016/j.ejrad.2019.06.003
Received 10 October 2018; Received in revised form 18 April 2019; Accepted 8 June 2019
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standard imaging method [13].

It is now recognized that PsA, [14] connective tissue diseases [15], and metabolic diseases [16], are associated with bone erosions in hands and feet on RX, but these diagnosis, not only based on radiography, are finally established by combination of specific clinical and biological features.

In patients aged over 50 years, the diagnosis of RA is usually established based on clinical and biological features. However, the diagnosis of erosive RA disease based on RX or US is sometimes difficult since bone erosions related to degenerative changes (osteoarthritis) may coexist with erosions due to RA. [1,17] Several studies have evaluated structural damages in RA, and especially erosions, in some selected joints or joint facets [18,19]. We have previously shown that US examination of 12 selected Joints (30 joint facets analysed) presented a better sensitivity and specificity that radiographic EULAR 2013 Definition of erosive RA based on SHS for erosions [20] But to our knowledge, no study has evaluated the best scenario in terms of sensitivity and specificity to establish the diagnosis of erosive RA on US with a limited number of joint examined.

This study aims to determine the best scenarios to establish the diagnosis of erosive RA on ultrasonography compared to OA patients, in terms of sensitivity, specificity and agreement with erosive RA on radiography.

2. Patients and methods

2.1. Population

All consecutive patients hospitalized between 2005–2016 for suspicion of RA in the department of Rheumatology in Nancy University Hospital were screened. Only patients fulfilling ACR 1987 and/or ACR/EULAR 2010 criteria for RA were selected for this study, patients fulfilling OA criteria served as control group. US and RX examination of hand and feet should be performed within 6 months. The only exclusion criterion was the presence of severe joint deformities that could prevent a complete appropriate clinical, US, and RX evaluation. A complete assessment of their disease was performed (clinical, biological, radiological, and ultrasound evaluations). For RA patients, data collection included the Disease Activity Score 28-joint count (DAS 28) and treatments at the time of evaluation (bDMARD, sDMARD, corticosteroids, and NSAIDs). For OA patients, no treatment has been registered.

2.2. Biological assessment

The following parameters were recorded: C-reactive protein level (CRP: normal value < 5 mg/L), erythrocyte sedimentation rate at the first hour (ESR: normal value < 5 mm), rheumatoid factor (RF) titres (normal value < 20 UI), and ACPA titres (normal value < 20 UI).

2.3. Radiography assessment

Postero-anterior views of hands and antero-posterior views of feet have been obtained according to the usual clinical practice recommendations for patients followed up for RA and for patients suffering from hand and/or feet OA [21]. RX analyses have been performed blindly from clinical and US information's. Two independent experimented readers (AP, MC) performed the Van der Heijde-modified Sharp score (SHS) for erosions (SHSe) with sub-scores for hands and feet. Based on this RX evaluation, patients were classified as erosive RA according to EULAR 2013 Definition [22]. Briefly, an erosive disease is defined when an erosion (defined as a cortical break) is observed in at least three separate joints at any of the following sites: proximal interphalangeal joints (PIP), metacarpophalangeal joints (MCP), wrist (counted as one joint), and metatarsophalangeal joints (MTP) on radiographs of both hands and feet. In the case of discordance between the two readers for a number of eroded joints less than or equal to three (corresponding to the threshold for erosive RA), a third reader (ICV) served as blinded adjudicator. For each patient, the SHSe corresponded to the mean score of the two or three readers.

2.4. Ultrasound assessment

Standardized US examinations were performed by senior US analysts (ICV, DL, JPS) after several sessions of harmonization for calibration of erosion. The equipment used throughout the study was the same: a Philips HD11 machine with a multi-frequency linear array transducer (5–12 MHz) with the focal length adjusted to the joint depth. US data were acquired at optimal technical conditions at 12 MHz (spatial resolution 0.1 mm) blinded to clinical, biologic, and radiologic findings.

Twelve pre-selected targeted joints have been systematically examined on B mode: metacarpophalangeal joints (MCPs) 2, 3, and 5 and metarsophalangeal joints (MTPs) 2, 3, and 5. MCP4 and MTP4 joints, less commonly affected by erosions in RA [13,23,24] ; MCP1 and MTP1 joints, more frequently damaged by degenerative changes or metabolic diseases, were not included.

2.4.1. Localization and grading of erosions

Erosions were searched on the dorsal (D), palmar/plantar (P) facets of each joint and on the lateral (L) facets when accessible (MCP2, MCP5 and MTP5). On each facet, erosion was defined as a cortical defect with an irregular bone surface, observed in two perpendicular planes (axial and longitudinal). Erosions were scored semi-quantitatively according to 4 grades: grade 0 = no erosion; grade 1 = single erosion < 2 mm in its largest dimension; grade 2 = single erosion ≥ 2 mm and < 3 mm in its largest dimension or no more than two erosions < 2 mm; and grade 3 = single erosion ≥ to 3 mm in its largest dimension or multiple erosions (n ≥ 2). The total US score for erosions (USSe) was the sum of erosion grades for all eroded joints and ranged from 0 to 90.

2.5. Statistical analysis

Characteristics of patients were described by number and percentage for categorical variables and by mean and standard deviation for continuous variables. For comparison, parametric statistics (Chi-square test, McNemar test, and ANOVA F-statistic) or non-parametric statistics (Fisher exact, Wilcoxon tests) were used when appropriate. The diagnostic performances (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) have been analysed. Sensitivity analyses of the threshold for dichotomizing the diagnosis of erosive RA based on RX and US were performed. Alpha risk was 5% for all analyses. These statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, N.C.).

The ethical committee of Nancy approved in June 2017 this study (Number of recording: R2017-17). The consents of the patients were given orally.

3. Results

3.1. Demographic characteristics of the population

During the study period, 168 patients were included. Among them, 122 patients (72.6%) belonged to the RA group and were separated into early RA (disease duration of less than 2 years, n = 32) and late RA (disease duration of 2 years or more, n = 90), and 46 patients (274%) belonged to the OA group. Gender and age (mean age: 54.9 ± 13.5 years for RA patients and 56.8 ± 9.6 for OA patients) did not differ between groups (p = 0.4204 and p = 0.3781 respectively). The demographic characteristics are detailed in Table 1.

Table 1
Characteristics of patients.

	Rheumatoid Arthritis		Rheumatoid Arthritis < 2 years		Rheumatoid Arthritis ≥2 years		Osteoarthritis	
	N = 122		N = 32		N = 90		N = 46	
	(72.6%)		(19.0%)		(53.6%)		(27.4%)	
	N(%)	Mean(SD)	N(%)	Mean(SD)	N(%)	Mean(SD)	N(%)	Mean(SD)
Age	122	54.9(13.5)	32	54.3(15.7)	90	55.1(12.7)	46	56.8(9.6)
Gender								
Male	34(27.9)		10(31.3)		24(26.7)		10(21.7)	21.7
Female	88(72.1)		22(68.8)		66(73.3)		36(78.3)	78.3
Disease duration (years)	122	7.1(7.2)	32	0.9(0.4)	90	9.3(7.1)	46	6.2(8.1)
Delay between RX and US (days)	122	0.6(6.9)	32	0.8(7.5)	90	0.5(6.7)	46	39.7(269.2)
NSAIDs	16(13.1)		1(3.1)		15(16.7)		0	0.0
Corticosteroids	68(55.7)		18(56.3)		50(55.6)		0	0.0
sDMARDS	94(77)		23(71.9)		71(78.9)		0	0.0
bDMARD	37(30.3)		2(6.3)		35(38.9)		0	0.0
ESR	121	22.5(20.2)	32	32.2(26.5)	89	19.1(16.3)	0	
CRP (mg/l)	122	10.8(22.6)	32	19.5(31.6)	90	7.7(17.6)	0	
ACPA	84(68.9)		21(65.6)		63(70.0)		0	0.0
ACPA (titers)	106	357.7(696.1)	27	526.1(893.5)	79	300.1(610.8)	0	
RF	70(57.4)		17(53.1)		53(58.9)		0	0.0
RF (titers)	98	88.4(161.8)	27	69.5(139.2)	71	95.5(170.0)	0	
DAS 28	117	3.6(1.4)	29	4.3(1.8)	88	3.4(1.2)	0	

N: number; SD: Standard deviation; NSAIDS: non-steroidal anti-inflammatory drugs, sDMARDs: synthetic DMARDS, bDMARDs: biologic DMARDS, ESR: erythrocyte sedimentation rate, CRP: C-.

Table 2
Distribution and prevalence of eroded joints in rheumatoid arthritis, early rheumatoid arthritis and osteoarthritis for joints evaluated on modified Sharp/van der Heijde score.

	Rheumatoid Arthritis (n = 122)	Osteoarthritis (n = 46)		Early Rheumatoid Arthritis (n = 32)	Osteoarthritis (n = 46)	
	Nb of eroded joint	Nb of eroded joint	p	Nb of eroded joint	Nb of eroded joint	p
WRIST	50	10	0.0722	5	10	0.7345
MCP1°	17	0	**0.0164**	2	0	0.0952
MCP2	23	1	**0.0168**	1	1	**0.0098**
MCP3	12	0	**0.0363**	1	0	0.4103
MCP4	4	0	0.5758	1	0	0.4103
MCP5	5	0	0.5758	1	0	0.4103
IPP1°°	0	0	–	0	0	–
IPP2	2	4	0.1269	2	4	0.9616
IPP3	6	5	0.3935	1	5	0.6401
IPP4	2	5	0.1269	0	5	0.2647
IPP5	1	0	1.0000	0	0	–
IP1	10	1	0.2884	3	1	0.5646
MTP1°°°	16	2	0.1592	1	2	0.7824
MTP2	20	1	0.0710	0	1	**0.0327**
MTP3	24	0	**0.0045**	3	0	**0.0452**
MTP4	17	0	**0.0127**	2	0	0.1652
MTP5	63	0	< **0.0001**	8	0	**0.0035**
Mean of eroded joint ± SD*	2.23 ± 3.1	0.63 ± 1.24	< **0.0001**	0.97 ± 1.58	0.63 ± 1.24	< **0.0001**
Mean of SHSe ± SD**	5.98 ± 11.09	1.09 ± 2.58	< **0.0001**	1.62 ± 3.09	1.09 ± 2.58	< **0.0001**

N : number ; SD : Standard Deviation, Mean SHSe: Mean Modified Sharp/van der Heijde score for erosion; MCP: metacarpophalangeal joints, IPP/IP: proximal Interphalangeal joints; MTP: metarsophalangeal joint; p : Chi-2 Test.
The results in bold are significative.

3.2. Radiographic evaluation

3.2.1. Reproducibility for SHSe

Among the 168 exams, 99 (58.9%) matched between the two readers for a number of eroded joints less than or equal to three. A third reading was necessary for 69 patients (41.1%) who were statistically younger (53.1 ± 11.2 vs 58.8 ± 13.6; p = 0.0035).

3.2.2. Characteristics of RX erosions

3.2.2.1. Prevalence, localization and severity of RX erosions. For the 168 patients 12 OA and 72 RA patients (12 early RA and 60 late RA) presented at least one erosion. Details of eroded joints in the two populations were presented in Table 2. On radiography, 29 eroded joints (1.0%) in the OA group and 272 (9.5%) in the RA group were identified (p < .0001). The mean SHSe was significantly different between OA and RA groups, and also between total population, early and late RA groups respectively (p < .0001) ((Table 2).

3.2.2.2. Discriminant joints between RA and OA. Compared to OA: MCP1, MCP2, MCP3, MTP3, MTP4 and MTP5 joints were significantly more frequently eroded in RA groups, and only MTP3 and MTP5 joints in early RA (see results in Table 2). Erosions of the MTP2 joints were more frequently observed in OA patients.

Table 3
Difference of prevalence for eroded joints between OA and RA and OA and early RA for joints evaluated on USSe.

		RA (n = 122) nb of eroded joint	OA (n = 46) nb of eroded joint	p	Early RA(n = 32) nb of eroded joint	OA (n = 46) nb of eroded joint	p
MCP2°	D	33	0	**0.0012**	2	0	0.0564
	P	26	0	**0.0037**	4	0	**0.0252**
	L	88	4	< **0.0001**	17	4	**0.0019**
	tot†	147	4	< **0.0001**	23	4	**0.0008**
MCP3	D	25	0	**0.0034**	2	0	0.0564
	P	3	0	0.5626	0	0	–
	tot	28	0	**0.0034**	2	0	0.0564
MCP5	D	17	0	**0.0453**	0	0	–
	P	7	0	0.1901	1	0	0.4103
	L	55	1	< **0.0001**	7	1	**0.0283**
	tot	79	1	< **0.0001**	8	1	**0.0396**
MTP2°°	D	6	1	0.6751	1	1	0.7938
	P	10	0	0.0634	1	0	0.4103
	tot	16	1	0.0727	2	1	1.0000
MTP3	D	6	0	0.3234	2	0	0.4103
	P	11	0	0.0634	1	0	0.4103
	tot	17	0	**0.0379**	3	0	0.4103
MTP5	D	33	1	**0.0026**	6	1	**0.0396**
	P	87	1	< **0.0001**	10	1	**0.0071**
	L	130	4	< **0.0001**	19	4	**0.0003**
	tot	250	6	< **0.0001**	35	6	**0.0009**
Mean of eroded joint ± SD*		4.4 ± 4.7	0.3 ± 0.4	< **0.0001**	2.3 ± 3.4	0.3 ± 0.4	< **0.0001**
Mean USSe ± SD**		10.0 ± 12.0	0.4 ± 0.7	< **0.0001**	4.3 ± 7.5	0.4 ± 0.7	< **0.0001**

Standard Deviation, **Mean of total Erosive Score US, ◊ Number of eroded joint, °MCP Metacarpophalangeal joints, °°MTP Metarsophalangeal joints, † Total, D: Dorsal, P: Plantar/Palmar, L: Lateral, p: Chi-2 Test.
The results in bold are significative.

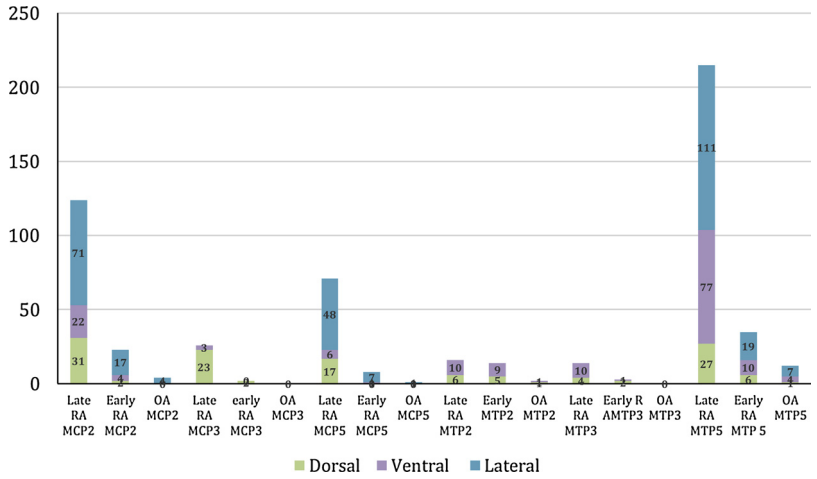

Fig. 1. Spatial localization of US erosion for each joint and for late rheumatoid arthritis (RA) (n = 90), early RA (n = 32) and osteoarthritis (OA) (n = 46) diseases. Dorsal (green), ventral (purple) and lateral (blue) joint facets of metacarpophalangeal (MCP) joints and metatarsophalangeal (MTP) joints.

3.2.2.3. Number of patients (OA and RA) responding to the definition of erosive RA regarding to EULAR 2013 Definition. In OA group, 12 patients (26.1%) presented at least one erosion, for whom 5 (10.8%) satisfied with EULAR 2013 Definition of erosive disease (Table 2). In the RA group, 72 patients (59.0%) presented at least one erosion for whom 42 (71.2%) satisfied with EULAR 2013 Definition of erosive disease (six (4.9%) in early RA and 36 (29.5%) in late RA). The sensitivity and specificity were calculated at 34.4% and 89.1%, respectively.

3.3. Ultrasound evaluation

3.3.1. Intra- and inter-examiner US reproducibility

Intra-examiner reproducibility was assessed on 11 RA patients according to two complete examinations per patient within 24 h. Inter-examiner reproducibility was assessed on 11 RA patients examined independently on the same day by each US operator. For intra-examiner reproducibility, the median value of the total US erosion score was 21 (range: 3–35) for the first exercise and 21 (range: 3–34) for the second. The intra-class correlation coefficient (ICC) values of the erosion US score for intra- and inter-examiner studies were 0.96 (CI95: 0.93–0.98) and 0.97 (CI95: 0.92–0.99), respectively. The inter reader reliability for the diagnosis of erosion was excellent (Gwet's AC1: 0.80)

3.3.2. Characteristics of erosions

3.3.2.1. Prevalence, localization and severity of US erosions. For the 168 patients, 12 (26.1%) patients and 95 (77.9%) patients (21 (22.1%) early RA and 74 (77.9%) late RA) were eroded in OA and RA groups, respectively. Details of eroded joints in the two populations were presented in Table 3. Twelve OA patients (26.1%) presented one erosion, and five patients had an erosion of grade 2. In RA patients, the distribution of erosions prevailed on lateral facets, independently of disease duration. MTP5 joints were the most frequently eroded joints (46.5%), followed by MCP2 (27.3%) and MCP5 joints (14.7%); details are presented in Figs. 1–3 and Table 3.

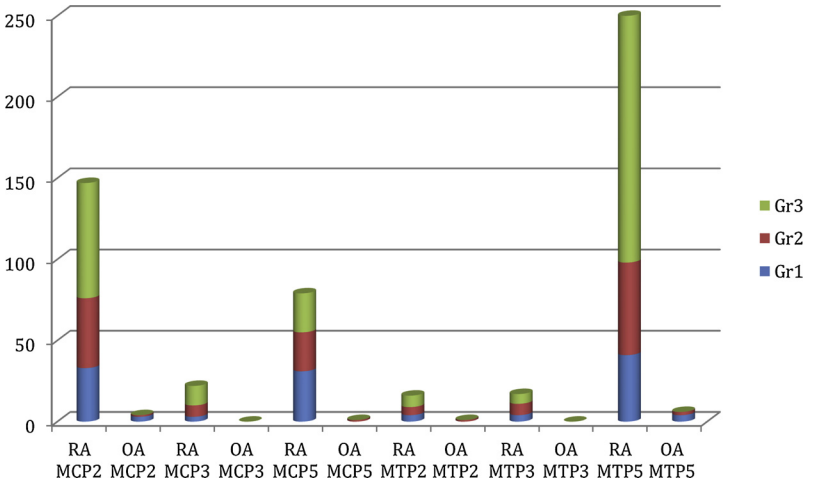

Fig. 2. Severity of US erosion for each targeted joints: grade 1 (blue) = single erosion < 2 mm in its largest dimension, grade 2 (red) = single erosion ≥ 2 mm and < 3 mm in its largest dimension or no more than two erosions < 2 mm; and grade 3 (green) = single erosion ≥ to 3 mm in its largest dimension or multiple erosions (> n = 2) for rheumatoid arthritis (RA) (n = 122) and osteoarthritis (OA) (n = 46). MCP: metacarpophalangeal joints, MTP: metatarsophalangeal joints.

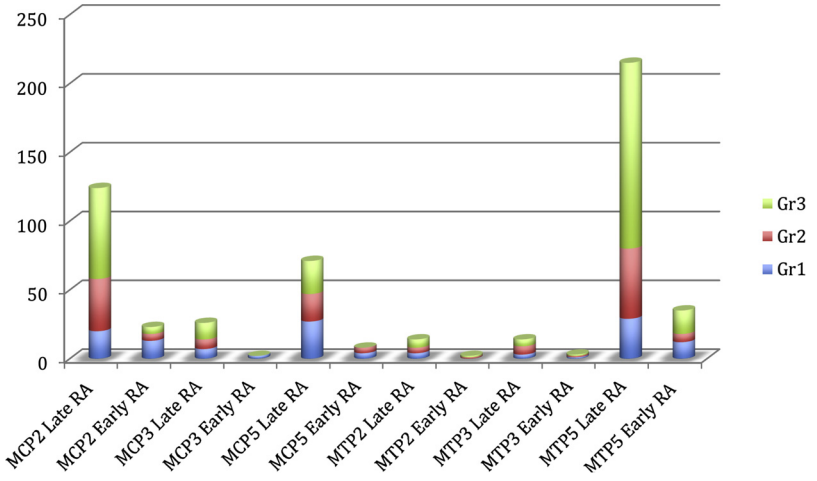

Fig. 3. Severity of US erosion for each targeted joints for late (n = 90) and early (n = 32) RA: grade 1 (blue) = single erosion < 2 mm in its largest dimension, grade 2 (red) = single erosion ≥ 2 mm and < 3 mm in its largest dimension or no more than two erosions < 2 mm; and grade 3 (green) = single erosion ≥ to 3 mm in its largest dimension or multiple erosions (> n = 2). MCP: metacarpophalangeal joints, MTP: metatarsophalangeal joints.

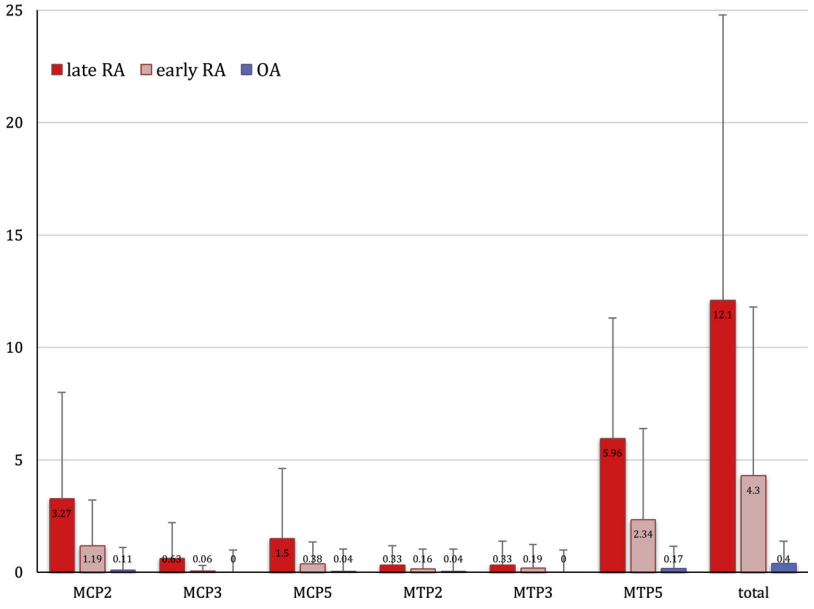

Fig. 4. USSe (ultrasound score for erosion) for each joint and for late rheumatoid arthritis (RA) (red) (n = 90), early rheumatoid arthritis (RA) (pink) (n = 32), and osteoarthritis (OA) (blue) (n = 46). MCP: metacarpophalangeal joints, MTP: metatarsophalangeal joints.

Table 4
Sensitivity (Se) and Specificity (Sp) of different scenarios (joints or joint facets selected) of eroded RA on US according to erosion of at least a grade 2 or at least two eroded joint facets.

		Erosion on US ≥ grade 2 at the joint facet level						RX+ (n = 42)	≥ 2 eroded joint facets on US						RX+ (n = 42)
Scenarios	Fac(n)*	RA°	Early RA	OA°°	Se	Sp	PPV	NPV	Ag%◊	RA	Early RA	OA	Se	Sp	PPV	NPV	Ag%
All joints of the USSe	**30**																
Number of patients eroded		**81**	**11**	**5**	**66.4**	**89.1**	**94.2**	**50.0**	**92.8**	**83**	**14**	**0**	**68.0**	**100**	**100**	**54.1**	**90.4**
MCP2 + MCP5 + MTP5	**18**																
Number of patients eroded		**79**	**11**	**4**	**64.7**	**91.3**	**95.2**	**49.4**	**92.8**	**81**	**14**	**0**	**66.4**	**100**	**100**	**52.9**	**90.4**
MCP2 + MTP5	**12**																
Number of patients eroded		**78**	**11**	**3**	**63.9**	**93.5**	**96.3**	**49.4**	**92.8**	**77**	**14**	**0**	**63.1**	**100**	**100**	**50.5**	**88.1**
MCP2L + MCP5L + MTP5 (P + L)†	**8**																
Number of patients eroded		**74**	**10**	**3**	**60.7**	**93.5**	**96.1**	**47.2**	**92.8**	**75**	**12**	**0**	**61.5**	**100**	**100**	**49.5**	**88.1**
MCP2L + MTP5 (P + L)	**6**																
Number of patients eroded		**74**	**10**	**2**	**60.7**	**95.6**	**97.4**	**47.8**	**92.8**	**73**	**12**	**0**	**59.8**	**100**	**100**	**48.4**	**88.1**

RX+: EULAR 2013 Definition; US: Ultrasounds; Se: sensitivi.
*Joint facets (number), ** total Erosive Score US (USSe) ± Standard Deviation, ◊ Agreement between RX and US for erosive RA disease, ° Rheumatoid Arthritis, °° Osteoarthritis.
†MCP : metacarpophalangeal joints, MTP metarsophalangeal joints, P: Plantar, L : Lateral.

The mean USSe was significantly different between OA and RA groups but also for total population, early and late RA groups respectively ($p < .0001$) (Table 3, Fig. 4)

3.3.2.2. Discriminant joints between RA and OA. Only MTP2 joint was not discriminant between RA and OA patients. (See Table 3).

In early RA, the three following joints: MCP2, MCP5 and MTP5 joints, were discriminant to establish a diagnosis of erosive RA on US (see Table 3). As well, the lateral joint facets alone were also discriminant for these three joints with the palmar joint facets of MCP2 joints and plantar joint facets of the MTP5 joints (see Table 3).

3.3.3. Definition of erosive RA on ultrasound

The presence of at least two eroded joint facets presented the better compromise in terms of sensitivity and specificity (68.0% and 100.0%, respectively) (Table 4). Considering the severity of the erosion at the joint facet level, whatever its localization, the presence of at least one erosion of grade 2 presented the best sensitivity (72.1%) and specificity (89.1%) ratios (Table 4)

Eighty-three RA (68.0%) (14 (16.9%) early RA and 69 (83.1%) late RA) and zero OA patients satisfied with definition of erosive RA with at least two US eroded joint facets. Considering the presence of at least one US erosion of grade 2 at joint facet level, 81 RA patients (66.4%) (11 (13.6%) early RA and 70 (86.4%) late RA) and five (10.9%) OA patients were classified with erosive disease (Table 4). In order to optimize the US examination (number of joint assessed, time of duration for US examination), different scenarios are presented in Table 4. These scenarios took into account the prevalence and the severity of erosion for each joint facet assessed in RA group in comparison to OA group. Whatever the scenario chosen, the specificity remained excellent (> 90%) with a sensitivity still preserved (> 59.8%). For the shorter scenario with only six targeted joint facets examined (MCP2L + MTP5P + MTP5L) 73 of 83 RA patients (87.9%) according to at least two eroded joint facets, and 74 of 81 RA patients (91.3%) according to at least one erosion of grade 2 at joint facet level, were still classified with erosive disease on US.

3.4. Diagnostic values of US compared to RX and agreements between RX and US for the diagnosis of erosive RA

According to radiographic assessment, 42 RA (six early RA and 36 late RA) and five OA patients satisfied with EULAR 2013 Definition for erosive RA. The agreements between RX and US, with all joints facets examined (N = 30), according to the two US thresholds (at least two eroded joint facets or at least one erosion of grade 2) were 90.4% and 92.8% respectively.

With only six targeted joint facets examined (MCP2L + MTP5P + MTP5L), the agreements between US and RX for the two US thresholds (at least two eroded joint facets or at least one erosion of grade 2), were 88.1% and 92.8% respectively (Table 4). These scenarios permitted to identify from 1.7 to 2 times more eroded patients with US in comparison to radiography ($p < 0.0001$). In early RA group, 12 and 10 patients were identified with erosive disease for at least two eroded joint facets and for at least one erosion of grade 2 at joint facet level, respectively, with an agreement between both imaging techniques of 88.6% and 92.8%, respectively (Table 4). In Fig. 5 was presented an example of early RA patient without EULAR definition of eroded RA with no erosion on radiography and at least three erosions (one erosion of grade 1 and two erosions of grade 2 and 3) detected at ultrasound examination. For patients with positive RX and negative US for erosion, radiographic assessment showed erosions on region explored on US (n = 10) and on region not explored on US: wrists (n = 6), MCP1 (n = 2), MCP4 joint (n = 1) and MTP4 joint (n = 1).

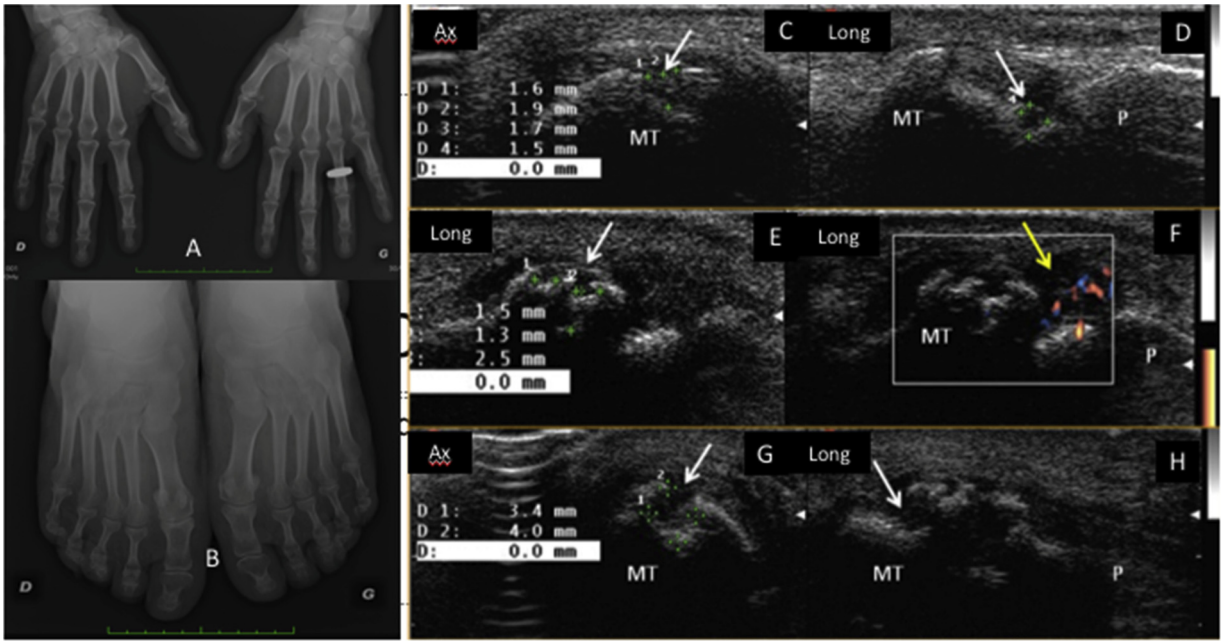

Fig. 5. Early RA patient without erosion on AP hands (A) and feet (B) radiography. On ultrasound examination 3 erosion were detected on axial and longitudinal scans: erosion (white arrow) of grad 1 of the plantar facet of the right MTPs 5 joint on B-mode scan (C,D), (E,F) and finally erosion of grade 3 of the lateral facet of the left MTPs5 joint (G,H).

4. Discussion

The aim of this study was to determine the most informative joints by US assessment to establish the diagnosis of erosive disease in RA, compared to OA patients in order to propose the best scenario for the diagnosis of erosive RA and to optimize US examination, according to two different approaches: 1) a minimal number of eroded joint facets (n = 2) 2) a minimal grade of severity for at least one joint facet eroded (grade 2).

Until now, ultrasonography in RA demonstrated its performance in terms of diagnosis of inflammatory lesions (synovitis, tenosynovitis) and its sensitivity to change to the treatment. [25–28] This technique also offers many advantages (accessibility, cost, and lack of irradiation) with good intra- and inter-reliabilities for assessing structural damage and especially erosion in RA and in other musculoskeletal diseases (PsA, hand OA) [9,11,29]. Our results confirmed excellent intra- and inter-ultrasonographer reliability with respect to grading erosions in patients examined in real life conditions [18,19,30–32]. In this study, US joint examination was limited at some selected joints because not all the joints evaluated using the SHS can be explored in clinical practice. We decided, as other authors have done, to exclude the wrist because of its anatomic characteristics that make it difficult to localize erosions with precision in axial and longitudinal planes, except for the ulnar styloid process, where detection of these erosion seems easier [30]. We also excluded: MCP1, MTP1 and all PIP joints because these joints may be eroded by other musculoskeletal diseases and especially by osteoarthritis (the most prevalent disease in patients over 50 years old) [19,23,33]. We excluded patients with severe joint deformities because this exam performs poorly in this situation and is inappropriate (joints not well visualized and erosion not clearly identified on two perpendicular planes) [34].

In late and early RA, we confirmed on US that, the MTP5 joints, the MCP2 joints, and then the MCP5 joints are the most prevalent eroded joints detected by ultrasound, especially in the lateral and plantar/palmar joint facets. When the severity of erosion was assessed by US, the MTP5 and MCP2 joints presented the most severe lesions, as shown by other studies. [30,34,35]. In OA patients, MCP2 followed by MTP5 joints was also the most frequently eroded joints with a prevalence varying from 5 to 13% according to the joint examined, but none of these joints was severely eroded [30]. In our study, five OA patients presented erosion of grade 2 (10.3%), whereas Zayat et al. [30] did not find severe erosion in OA patients. With a threshold of two eroded joint facets, whatever the grade of severity observed, we calculated a sensitivity of 68.0% with a specificity of 100.0%. According to the most prevalent and the most severe joint facets eroded, we scheduled five scenarios, varying between 30 joint facets and six joint facets assessed. Whatever the scenario chosen, the specificity remained excellent (> 90%) with a sensitivity superior to 59.8%. With only six joint facets examined, less than 15% of patients with erosive RA disease, diagnosed on all joint facets assessed were not identified as erosive RA disease. The agreement between RX (three joints eroded) and US was still excellent over 88.1%. In the literature, four scores of US erosions were compared to radiographic assessment: two according to the SHS, [18,28], one with Steinbrocker score [36] and one with a short version of the SHS with a selection of seven joints [37]. In these studies, where radiographic evaluation were performed by one or two readers the authors confirmed the superiority of ultrasound to detect erosions but they were unable to define a threshold from which an erosive RA disease on US can be established due to the lack of a control group.

On radiography, the diagnosis of erosive RA in hands and feet is routinely performed in clinical practice. Moreover, RX serves as the gold standard for diagnosis of erosive disease if at least three selected joints are eroded. [22] The diagnosis of eroded disease in RA is crucial since structural damages are associated with poor functional outcome and considered as poor prognostic factors leading to a more aggressive therapy. RX presents many advantages: the views and the technical parameters are well defined and the diagnosis of erosive RA is easily established after a careful reading performed for few seconds. The modified SHS is considered one of the standard methods for assessing structural effects of RA DMARDs (synthetic or biologic) in clinical trials because it presents excellent intra- or inter-reader reliabilities and a good sensitivity to change [8,38]. To limit reading biases, two senior readers of the ESPOIR's cohort [18] blindly assessed the Sharp-erosion score, and an adjudication was made by a third senior reader, permitting us to retain the diagnosis of 42 RA patients with erosive disease and of five patients with erosive OA. On the 44 joints assessed, MTP5 and

wrists joints were most frequently eroded as described in the literature in RA [39]. Finally, the EULAR task force retained the diagnosis of erosive RA on radiography by the presence of at least three eroded joints in two cohorts of early arthritis with sensitivities and specificities calculated at 15–29% and at > 80% respectively. [18,40]. With patients with hand OA considered as control, we calculated a sensitivity and a specificity at 34.4% and 89.1%, respectively.

In 2000, Wakefield et al [13] demonstrated that ultrasonography permits to detect, at the joint level, 6.5 times more erosions in early RA disease and 3.5 times more erosions in late RA, than radiography. The superiority of ultrasound was confirmed in other studies [24,41] but also when CT scans served as the gold standard [42]. Our study demonstrated, on 30 joint facets examined, that ultrasound detected 2.0 times more eroded RA patients than radiography with a threshold of at least two eroded joint facets and 1.9 times more patients than radiography according to Sharp's score approach, with a threshold of at least one erosion of grade 2 at joint facet level with excellent specificities (100.0% and 89.1%, respectively). With the scenario of six targeted joint facets examined (MCP2L + MTP5P + MTP5L), the ratio remained stable with 1.7 times more patients with erosive disease on US than RX and may reduce the time of the US examination from 20 to 10 min. When early RA were examined, ultrasonography is able to detect two times more erosive RA than radiography. This discrepancy is explained by the presence of erosions on wrist on radiography, joint difficult to be examined on US due its anatomic structure. In this situation, both RX and US seems to be complementary and should be performed in order to optimize the diagnosis of erosive RA.

This pilot study performed by trained sonographers required the development of an external validation process such as the OMERACT filter. The sensitivity to change should also be tested, and the relationship between bone erosion and joint inflammation at the joint level and in the different scenarios should be also investigated. Of course, radiographic and ultrasonographic patterns of erosion in other musculoskeletal diseases were not evaluated in this study and could be evaluated in the future. Finally, joint space assessment, not performed in this study and recently validated by Mandl et al., [43] should also be investigated to improve the structural approach by US.

To conclude, we demonstrated that bone erosions assessed by US were reliable and may be observed in both diseases, with a higher prevalence and severity in RA. US erosion assessment of only six targeted joint facets (MCP2L + MTP5P + MTP5L) permit to detect 1.7 times more patients with erosive RA than RX with a good sensitivity (> 59.8%), an excellent specificity (> 95.6%) and an excellent agreement between both imaging techniques (> 88.1%). More in early RA than in established RA, US examination and radiography should be performed together in order to optimize the diagnosis of erosive disease.

Acknowledgment

The text has been proofread by Springer (number P9Y4G1TL).

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