



## Original Investigation

# Development of an ultrasound set for early diagnosis of rheumatoid arthritis: First steps



Ben Abdelghani Kawther<sup>a,g</sup>, Miladi Saoussen<sup>a,g,\*</sup>, Mahmoud Ines<sup>b</sup>, Ajlani Houda<sup>c,g</sup>, Bahiri Rachid<sup>d,g</sup>, Haddouche Assia<sup>e,g</sup>, Harifi Ghita<sup>h</sup>, Slimani Samy<sup>f,g</sup>, Laatar Ahmed<sup>a</sup>

<sup>a</sup> Rheumatology Department, Faculty of Medicine of Tunis, University of Tunis El Manar, Mongi Slim Hospital, La Marsa, Tunis, Tunisia

<sup>b</sup> Rheumatology Department, Faculty of Medicine of Tunis, University of Tunis El Manar, Charles Nicolle Hospital, Tunis, Tunisia

<sup>c</sup> Rheumatology Department, El Yasminet Hospital, Ben Arous, Tunisia

<sup>d</sup> Rheumatology Department, El Ayachi Hospital, CHU Rabat-Salé, Morocco

<sup>e</sup> Department of Rheumatology, Ben Aknoun Specialized Hospital in the Musculoskeletal System, Ben Aknoun, Algeria

<sup>f</sup> Rheumatology Department, Atlas Clinic of Rheumatology, Batna, Algeria

<sup>g</sup> Department of Rheumatology, Comité d'Experts Maghrébins en Imagerie Rhumatologique, Rabat, Morocco

<sup>h</sup> Rheumatology Department, HBMC Rheumatology Clinic, Emirates Hospital Group, Dubai Health Authority, Dubai, United Arab Emirates

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## ABSTRACT

**Introduction/Objective:** Early diagnosis of rheumatoid arthritis (RA) can improve the prognosis of the disease by reducing joint destruction and achieving a better rate of remission. Musculoskeletal ultrasound (US) has become a potent tool to detect synovitis and erosions. However, until now, there has been a lack of consensus on the US scoring system to help in diagnosing RA early. The purpose of our study was to elaborate a US set suitable for classifying RA patients with inflammatory arthralgia or expressing synovitis and who did not satisfy ACR/EULAR criteria, called "USSRA" (UltraSound Set for Rheumatoid Arthritis).

**Materials and methods:** A multistep study was conducted. A preliminary set of joints, tendons, and erosions to include in the USSRA were identified through a deep literature screening. The final step of this study was the validation of the final set by international experts in US using a Delphi process.

**Results:** The preliminary set included 20 joints, 16 tendons, and 8 erosion sites for assessment. After the Delphi process, the changes were to add an assessment of two additional wrist joints and remove one. As for the tendons, two sites were removed from the final set. No changes were proposed for the section erosions. The elementary lesions and scoring system were clarified. The final USSRA forms include 18 joints, 12 tendons, and 8 sites of erosion.

**Conclusion:** The USSRA is a novel diagnostic tool proposed for detecting early RA in routine practice. The next step will be to assess the reliability of this set in a patient-based exercise.

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\* Corresponding author.

E-mail address: [saoussenmiladi@gmail.com](mailto:saoussenmiladi@gmail.com) (M. Saoussen).

## Desarrollo de un equipo de ultrasonido para el diagnóstico precoz de la artritis reumatoide: primeros pasos

### R E S U M E N

#### Palabras clave:

Sinovitis  
Tenosinovitis  
Erosión  
Técnica Delphi  
Diagnóstico precoz  
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**Introducción/Objetivo:** El diagnóstico precoz de la artritis reumatoide (AR) puede llevar a que el pronóstico de la enfermedad mejore, puesto que se puede reducir la destrucción articular y obtener una mejor tasa de remisión. La ecografía musculoesquelética (US) se ha convertido en una potente herramienta para detectar sinovitis y erosiones; sin embargo, falta un consenso sobre el sistema de puntuación de ultrasonido para ayudar a diagnosticar la AR de manera temprana. El propósito del estudio que aquí se presenta fue elaborar un conjunto de ultrasonido adecuado para clasificar pacientes con AR con artralgia inflamatoria o expresión de sinovitis y que no cumplieran los criterios ACR/EULAR, denominado *UltraSound Set for Rheumatoid Arthritis* (USSRA).

**Materiales y métodos:** Se llevó a cabo un estudio de varios pasos. Se identificó un conjunto preliminar de articulaciones, tendones y erosiones para incluir en la USSRA mediante una revisión profunda de la literatura. El paso final de este estudio fue la validación del conjunto final por parte de expertos internacionales en Estados Unidos utilizando un proceso Delphi.

**Resultados:** El conjunto preliminar incluyó 20 articulaciones, 16 tendones y 8 sitios de erosión para su evaluación. Después del proceso Delphi, los cambios fueron: agregar la evaluación de 2 articulaciones de muñeca adicionales y eliminar una. En cuanto a los tendones, se eliminaron 2 sitios del conjunto final. No se han propuesto cambios para la sección de erosiones. Se aclararon las lesiones elementales y el sistema de puntuación. Los formularios finales de la USSRA incluyen 18 articulaciones, 12 tendones y 8 sitios de erosión.

**Conclusión:** La USSRA es una herramienta diagnóstica novedosa propuesta para la detección precoz de la AR en la práctica habitual. El próximo paso será evaluar la confiabilidad de este conjunto en un ejercicio basado en el paciente.

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## Introduction

Musculoskeletal ultrasound (US) has become a widely used tool for monitoring rheumatoid arthritis (RA).<sup>1</sup> It is considered as a sensitive imaging modality for detection of subclinical synovitis and tenosynovitis, since this imaging tool helps not only to assess but also to quantify these findings.<sup>2</sup> Besides, US is a more reliable modality than plain radiography to detect joint erosions in hands.<sup>3</sup>

Several studies reported that US is a more sensitive and specific technique for the detection of RA as compared to clinical assessment and laboratory tests.<sup>4-7</sup> Various scoring systems are available to evaluate RA activity, but only a few were designed to establish to classify patients with RA.<sup>8,9</sup> Different scores were listed by the review of Nam et al.<sup>9</sup> These scores aimed specially to demonstrate the contribution of US to detect infra-clinical synovitis and to diagnose RA. However, till now, there is a lack of an optimal set of joints that should be imaged to diagnose RA at an early stage.

For this purpose, we propose the “USSRA” (Ultrasound Set for Rheumatoid Arthritis) as a consensual composite US set to be used in case of suspicious RA to help physicians to the final diagnosis.

## Methods

### Study design

As a first step, we identified through a literature review all studies concerning the US added value in undifferentiated arthritis or early RA. Relevant studies including joints, tendons, or erosions were identified and screened to elaborate the preliminary USSRA set (pUSSRA). Thereafter, a Delphi process was conducted through international US experts to assess the final USSRA set.

A separate paper will be devoted to the final step of USSRA validation. It will consist in a patient-based study to assess the reliability among rheumatologists of the USSRA set.

### Delphi process

A two-round Delphi consensus was conducted through a GoogleForm® questionnaire sent by email to 63 rheumatologists, from various countries. The form was sent in French or in English depending on their origin. The survey was sent to experts in US who had EULAR certification or they declared interest on OMERACT US task force.

The first questionnaire included 49 items divided into three sections: joints, tendons, erosions. The participants were asked to respond within two weeks. A reminder email was sent to non-responders after one week. The investigators had to rate their level of agreement for each item using a scale ranging from 1 to 9, where 1 corresponded to totally disagree and 9 to totally agree. Additional free spaces were reserved for additional suggestions at the end of each section.

An agreement was considered if more than 75% of investigators attributed a level of agreement more than 7 and the item was included in the final USSRA set from the first round. A disagreement was considered if more than 75% of participants rated a level of agreement less than 4 and the item was excluded definitely from the USSRA fiche. If the statement did not respond to one or another of the cited situations above, it was included into the second round of the survey.

The second questionnaire was sent two weeks after starting the Delphi process. The items were divided into the same three sections. After one week, a reminder email was also sent to non-responders. The statement rated more than 7 by more than 75% of participants were retained in the final USSRA set.

## Ethical considerations

No patient was involved in this study. So, no ethical permission was required.

## Highlights

- A consensual ultrasound set was elaborated based on literature search and a Delphi process among experts on ultrasonography.
- Assessing hands, feet, and symptomatic joints for synovitis, tenosynovitis, and erosions may help to diagnose rheumatoid arthritis at a very early stage of the disease.

## Results

### The preliminary USSRA set

The pUSSRA form included the first topic of synovitis (which was defined as the presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal): assessment of wrists, from first to fifth metacarpophalangeal (MCP), to second and third proximal interphalangeal (PIP) joints, second and fifth metatarsophalangeal (MTP) bilaterally dorsal view using the semi-quantitative scale EULAR-OMERACT.<sup>10</sup> Tenosynovitis were defined as an abnormal anechoic and/or hypoechoic tendon sheath widening, which can be related both to the presence of tenosynovial abnormal fluid and/or hypertrophy and which may be associated to Doppler signs. Locations of tenosynovitis to hold were ulnar extensor of the carpe, common digital extensor (fourth compartment), first to fifth digital flexor, and posterior tibial tendon bilaterally using a binary scale. Erosions were only considered if they exceeded 2 mm, in ulna, dorsal, lateral, and palmar view in second MCP, dorsal,

medial and palmar view in fifth MCP, and dorsal, lateral and plantar view in fifth MTP bilaterally using a binary scale.

### Delphi process

At the first round, the response rate was 29%. Responders were from various countries around the world: Algeria, England, France, Italy, Lebanon, Mexico, Morocco, Netherland, Romania, Spain, Switzerland. Overall, there was an agreement in 31 items. A disagreement was noted in 3 statements. Fifteen items were exposed in the second round. Four additional items were proposed by participants and added to the second round for agreement. After the second round, the response rate was 94%, only one investigator did not respond to the questionnaire.

After the two rounds of Delphi process, comparatively to the pUSSRA, the changes were:

- Adding assessment of two additional joints in wrist, the medio-carpal and radio-ulnar joints, besides the radio-carpal joint proposed.
- Adding symptomatic joints (tender or swollen joint).
- Removing the study of the first MCP.
- Concerning tendons, the first and fifth flexor were removed from the final set.
- No changes have been proposed for the section erosions.
- The final USSRA form include 18 joints, 12 tendons and 8 sites of erosions. Symptomatic joints, tender or swollen ones, were added. The two rounds of Delphi process are summarized in [Table 1](#).

## Discussion

Across this study, we propose USSRA as an imaging tool to classify patients with RA even if they did not respond to the ACR/EULAR criteria. This set was developed after deep review of literature and through a Delphi process including opinions of international experts in US. This tool is suitable for patients with undifferentiated arthritis (UA) and is not adapted for monitoring RA activity. Using this set should be associated to the opinion of the rheumatologist to diagnose RA since there is no score or a cut-off using this tool in this step. Indeed, any abnormality found using USSRA may be suggestive for RA. Some findings might be more suggestive for the diagnosis as an ulnar tenosynovitis or especially an erosion.

Its a fact: the sooner a diagnosis of RA is made, the better outcomes are reached.<sup>11</sup> In RA, remission is more likely to be obtained in the first period of development of the disease called 'window of opportunity'. Old publications supported that this period extended to the first two years of the disease.<sup>12</sup> However, in recent publications this therapeutic window corresponded only to the pre-RA phase.<sup>13</sup> Imaging modalities are useful for early diagnosis of RA and are also recommended by current guidelines.<sup>14</sup>

US and magnetic resonance imaging (MRI) are sensitive modalities used for diagnosis of RA. MRI has a high cost and is not available in all clinical centres in our country. In the other hand, US is an inexpensive tool, non-irradiating, with good intraobserver and interobserver reproducibility and reliability

**Table 1 – Results of the two round Delphi process for elaborating USSRA.**

	First round			Second round	
	Median	>7 (%)	<4 (%)	Median	>7 (%)
<b>Joints</b>					
Wrist synovitis (radio and medio carpal joint)	9	94	0		
MCP 1 synovitis	6	31	36	7	55
MCP 2 synovitis	9	100	0		
MCP 3 synovitis	9	100	0		
MCP 4 synovitis	8	78	15		
MCP 5 synovitis	9	78	10		
PIP 2 synovitis	8	78	5		
PIP 3 synovitis	8	78	0		
MTP 2 synovitis	7	57	15	8	77
MTP 5 synovitis	9	84	10		
MCP joints scanned in palmar side	6	42	31	2	22
MCP joints scanned in dorsal side	9	94	0		
PIP joints scanned in palmar side	7	52	15	4	33
PIP joints scanned in dorsal side	9	78	5		
MTP joints scanned in plantar side	4	10	84		
MTP joints scanned in dorsal side	9	94	5		
Assessment of effusion	7	78	10		
Grading synovitis in “binary mode”	5	15	42	2	22
Grading synovitis in “Szkudlarek mode”	7	52	26	4	22
Grading synovitis in “PDUS mode”	9	84	5		
Assessing synovitis in other joints than cited	7	84	5	Inferior radio-ulnar joint	83
				Elbow	33
				Knee	46
				Symptomatic joints	94
<b>Tendons</b>					
First flexor tenosynovitis	5	26	52	5	27
Second flexor tenosynovitis	9	84	0		
Third flexor tenosynovitis	8	78	5		
Fourth flexor tenosynovitis	8	78	15		
Fifth flexor tenosynovitis	8	57	31	7	55
Common extensor tenosynovitis (fourth compartment)	8	78	10		
Ulnar extensor tenosynovitis (sixth compartment)	9	84	5		
Posterior tibial tenosynovitis	8	78	5		
Grading tenosynovitis in “binary mode”	3	10	78		
Grading tenosynovitis in “semi-quantitative mode”	8	84	5		
Assessing tenosynovitis in other sites	6	42	37	Fibular	50
<b>Erosions</b>					
Erosions in MCP 2	9	94	0		
Erosions in MCP 5	9	94	0		
MCP erosions scanned in palmar side	9	84	5		
MCP erosions scanned in lateral side	9	84	0		
MCP erosions scanned in dorsal side	9	84	0		
Erosions in ulnar styloid	9	100	0		
Erosions in MTP 5	9	100	0		
MTP erosions scanned in plantar side	9	94	0		
MTP erosions scanned in lateral side	9	78	0		
MTP erosions scanned in dorsal side	9	94	0		
To be considered as an erosion, the defect should exceed 2 mm	8	74	26		
Assessing erosions in other sites	6	21	78		

MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; MTP: metatarsophalangeal joint.

for the detection of synovitis<sup>10</sup> and tenosynovitis.<sup>15</sup> Moreover, all our rheumatology departments are provided with an ultrasound device and count at least one physician graduated in US. Thus, our interest in developing a national unified US set to detect RA earlier has motivated this study.

Regarding synovitis, both grey scale (GS) and PD mode were required. In fact, each of them has proven its importance

in reclassifying UA to RA. Regarding GS, over a study of 60 patients (1560 joints) of UA, its presence was associated with progression to RA, HR 1.25 [1.07–1.45] for the number of joints with GS  $\geq$  grade 2 after adjustment for swollen joints.<sup>16</sup> In addition, detection of PD signals increased the probability of development of RA. Within a study of 149 recent-onset UA, after 12 months of follow, evolution to established RA had

an OR of 17.5 [4.7–65.5] if there were 2 or 3 joints with PD and 48.7 [8.7–271.7] if more than 3 joints have PD signals.<sup>8</sup> PD was also associated to reclassifying UA to RA as in a study of seronegative arthritis, PD  $\geq 1$  for at least one joint contributed to the diagnosis of RA using ACR/EULAR criteria (OR 20.00,  $p \leq 0.001$ ).<sup>17</sup>

For synovitis, USSRA included assessing of at least 18 joints: wrists (radio-ulnar, radio and medio-carpal joints), from 2nd to 5th MCP, 2nd and 3rd PIP, 2nd and 5th MTP bilaterally. Symptomatic joints will be added if found. In previous studies, joint's sets used to detect early RA included from 18 to 38 joints,<sup>9</sup> but none used the same set as we did. Wrists joints were always included in US sets. Indeed, synovitis of carpal joints as identified by MRI in a study of 45 patients with untreated recent-onset polyarthritis were the most powerful predictors of progression towards RA (OR 3.64, 95% CI 1.12–11.84).<sup>18</sup> Regarding MCP, the first one was excluded from analysis in numerous studies since it is not a specific site of RA.<sup>8,18,19</sup> As per PIPs, the first one was also excluded in some studies.<sup>18–20</sup> The fifth one was excluded in a single study in order to reduce the examination time.<sup>19</sup> Therefore, for hands joints, a systematic review showed that the diagnostic test accuracy of US compared with MRI for the detection of synovitis in RA patients was as follow for wrist MCP and PIP: OR 11.6 (95% CI 5.6–24), 28 (95% CI 12–66) and 23 (95% CI 6.5–84) respectively.<sup>21</sup> Thus, our interest in US hands scanning in USSRA fiche.

Shoulders, elbows, knees, and ankles have been included in 2 studies.<sup>22,23</sup> But they did not prove their reliability in detecting RA.<sup>23</sup>

Using USSRA, assessing synovitis should be performed in dorsal view as agreed on by all experts after the Delphi process. The dorsal view was more sensitive than palmar one in detecting GS and PD synovitis in MCP and PIP.<sup>24</sup>

After two rounds of Delphi process, synovitis should be graded using the semiquantitative scale EULAR-OMERACT. In the literature, among a study of 840 joints and 700 tendons of 70 patients who underwent MRI and US examination of MCP (from 2nd to 5th) and MTP (from 1st to 5th), compared to MRI, Szkudlarek scale was more sensitive (68–91%) but EULAR-OMERACT was more specific (80–98%) in detecting synovitis.<sup>25</sup> Effusion was not considered in our set since it can be present even in healthy patients.<sup>26</sup> Additionally, the newest EULAR-OMERACT taskforce stipulated that synovitis was defined regardless of presence of effusion.<sup>27</sup>

Regarding tendons, our set included assessing ulnar extensor of the carpe, common digital extensor (fourth compartment), second to fourth digital flexor, and posterior tibial tendon bilaterally. Previously, tendons have been rarely assessed in early RA. Tenosynovitis of wrists and MCP joints was one of the earliest inflammatory features in patients with early RA.<sup>2</sup> In MRI, which is considered as the gold standard imaging tool for assessing tendons, digital flexor tenosynovitis were strongly predictive of early RA.<sup>28</sup> In another study, digital flexor tenosynovitis was identified by MRI on multivariate logistic regression (OR 5.09) after a follow-up of 12 months of 45 patients with early UA.<sup>18</sup> This findings were proven even using US in a study of 100 patients with UA, tenosynovitis of flexor digital tendons were more prevalent in the RA group compared with the resolving arthritis group in GS and PD (OR

4.455 [1.892–10.488],  $p \leq 0.001$ ).<sup>29</sup> In our study, after Delphi process, assessing, first and fifth flexor tendons were excluded. However, all digital flexor showed the same predictive value of developing RA in a study of 100 UA.<sup>29</sup>

Regarding common digital extensor, this same study demonstrated that RA patients were more likely to have wrist extensor US tenosynovitis (6 compartments) with both GS and PD.

Common digital extensor was not associated with progression to RA, in contrast with ulnar carpal extensor which has the highest predictive of RA in the very early stage of the disease (OR 6.07 [2.49–14.82],  $p \leq 0.001$ ).<sup>29</sup>

Regarding feet tendons, a comparative study of 432 ankles of patients with RA and 400 ankles of healthy subjects has proven that posterior tibial tenosynovitis was the most frequent US abnormality in RA patients.<sup>30</sup>

Erosions were considered in USSRA only if they exceeded 2 mm in ulna, 2nd and 5th MCP bilaterally and 5th MTP bilaterally. A circumferential assessment for all accessible faces are requested as for MCP in dorsal, lateral and palmar sides and for MTP in dorsal, lateral and plantar sides. A binary scale is used. In fact, erosions may be present at early stage of the disease.<sup>31</sup> US has a sensitivity similar to MRI to detect erosions<sup>32</sup> especially for joint surfaces easily available during the examination. The four targeted locations: 2nd, 5th MCP, 5th MTP joints and distal ulna was highly specific for RA with a specificity of 97.9%.<sup>33</sup> The OMERACT definition did not encompass the size. However, the most frequently used mensuration was 2 mm which enhanced difference from normal variation in bone surfaces.<sup>33</sup> A semi-quantitative score is available for erosions, it might be a useful tool to assess follow-up.<sup>34</sup> However, concerning diagnosis, lack of consensus, a binary scale would be preferable as voted through the Delphi process.

To the best of our knowledge, this is the first study that has assessed an US set to detect early RA through a Delphi process among international experts. Some limitations should be noted. The response rate to our questionnaire was poor (29%, 18 experts). However, it is worth mentioning that none of our national US practitioner was affiliated to international US committee and we did not have any relationship with any of our responders. Furthermore, according to French consensus of “Haute Autorité de Santé”, development of recommendations through a Delphi process requires from 9 to 15 raters.<sup>35</sup> Another weakness of our study was the absence of discussion with international experts about their choices when responding to the questionnaire as we may discussed why we should dismiss study of fifth digital flexor. Also, the proposed set seem to be time-consuming since it includes 18 joints, 12 tendons and 3 sites of erosions. For assessing the pUSSRA, our local team spent on average of 26 min. This period would be decreased because some sites were excluded from the final set.

In conclusion, we propose the USSRA for detecting early RA in routine practice. The next step planned would be assessing the reliability of this set in a real patient study.

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## Conflict of interest

None.



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