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Invited Review

Ultrasound in the evaluation of rheumatoid arthritis

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Abstract

In the last two decades, ultrasound has been fully implemented in the diagnosis and management of rheumatoid arthritis. Several studies have been published that have demonstrated better availability of this technique in the identification of elementary inflammatory joint and tendon injuries, as joint and tendon sheath synovial hypertrophy, joint effusion, and Power Doppler signal. Ultrasonography has good properties to identify changes with different treatments, have predictive value for relapse in patients in clinical remission and in structural damage. Furthermore, ultrasound tools have been developed that allow prospective evaluation of patients. Joint and tendon ultrasound evaluation indexes have been used for disease diagnosis and monitoring. Initially, indexes have been integrated only for joint, but more recently have appeared mixed indexes, integrated for ultrasound evaluation and other types of variables. There are still important objectives to be achieved to complete the development of ultrasound in rheumatoid arthritis, which makes ultrasound a great aid tool in decision-making in clinical practice.

Keywords: Ultrasonography, index, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) requires constant clinical monitoring. Thus, we have seen how in recent years, imaging techniques such as magnetic resonance imaging (MRI) and ultrasound (US) have been progressively incorporated into disease control, providing information on both activity and subclinical synovitis in patients in clinical remission. Ultrasound is being the most widely used due to its accessibility, the good quality of the images obtained, and the absence of contraindications in clinical practice.

The widespread use of ultrasound in rheumatoid arthritis is due to the great sensitivity offered in detecting synovitis compared to physical examination.[1] It can accurately assess two main elements of synovitis: hypertrophy and synovial effusion.[2] The effusion is visualized as an anechoic area that can be compressed with the pressure of the transducer, while the synovial hypertrophy is visualized as a usually hypoechoic material, barely compressible, both located within the articular capsule.[2] Both effusion and synovial hypertrophy are evaluated primarily on the grayscale, and Power Doppler (PD) is also used to show the inflammatory activity of synovial hypertrophy, by detecting microvascularization in the inflamed synovium.[3] Power Doppler has predictive value in relation to the radiological progression of synovitis[4,5] and flares of the disease.[6,7] Furthermore, in the setting of early arthritis, ultrasound may help to perform an accurate and earlier diagnosis of rheumatoid arthritis, contributing to the initiation of an effective intervention.[8]

It is noteworthy that the quantification of the degree of synovitis helps physicians in monitoring the disease and evaluating the response to treatment. Various methods have been developed for the ultrasound quantification of both synovial hypertrophy and effusion in recent years. Initially, binary scales (presence–absence) were used,[9] and later several semiquantitative scores were created that evaluated hypertrophy and synovial effusion both individually and in combination (Figures 1-4).[10,11] Other methods have been based on the measurement of the volume and depth of the synovium.[12] Regarding synovial effusion, it has recently been considered not to include it within the inflammatory component,[13] as it is valued as an inconsistent finding, since it can be detected frequently in healthy individuals or in joints of patients with inactive RA.[14,15] Just as the study of synovial vascularization using Power Doppler, as mentioned, has shown its predictive value for subsequent flares and for the development of erosions,[12–15] it is not clear what degree of gray-scale synovial hypertrophy indicates clearly a pathological finding, since joints of healthy patients may present a low level of gray-scale synovial hypertrophy.[16] To date, the most frequently used method in clinical practice for ultrasound quantification of synovitis is the semiquantitative scoring system for the degree of synovial hypertrophy and synovitis proposed by

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Table 1. Main characteristics of ultrasound indexes published.

Year	Reference	Index type	GS and/or PD	Semiquantitative	Joints	Tendons	US joint and tendons number	Joint/tendon arbitrary election
2003	Szkudlarek et al.[11]	SUI	GS + PD	Yes	Yes	No	5	Yes
2004	Taylor et al.[20]	SUI	GS + PD	Yes	Yes	No	10	Yes
2005	Naredo et al.[1]	SUI	GS + PD	Yes	Yes	No	60	No
2005	Scheel et al.[10]	SUI	GS + PD	Yes	Yes	No	8	Yes
2008	Hameed et al.[21]	SUI	GS + PD	Yes	Yes	No	20	Yes
2008	Ozgocmen et al.[22]	SUI	GS + PD	Yes	Yes	No	14	Yes
2008	Naredo et al.[18]	SUI	GS + PD	Yes	Yes	No	44	No
2009	Scire et al.[6]	SUI	GS + PD	Yes	Yes	No	44	Yes
2009	Backhaus et al.[19]	SUI	GS + PD	Yes	Yes	No	7	Yes
2009	Dougados et al.[23]	SUI	GS + PD	Yes	Yes	No	38	Yes
2010	Balsa et al.[24]	SUI	GS + PD	Yes	Yes	No	42	No
2016	D'Agostino et al.[25]	SUI	GS + PD	Yes	Yes	No	22	No
2016	D'Agostino et al.[26]	SUI	GS + PD	Yes	Yes	No	44	No
2016	Haavardsholm et al.[27]	SUI	GS + PD	Yes	Yes	No	28	Yes
2016	Dale et al.[28]	SUI	GS + PD	Yes	Yes	No	14	Yes
2012	Damjanov et al.[29]	MUI	GS + PD	Yes	Yes	No	28	Yes
2018	Salaffi et al.[30]	MUI	GS + PD	Yes	Yes	No	10	Yes
2019	de Agustín et al.[31]	MUI	GS + PD	Yes	Yes	Yes	14	No

SUI, simplex ultrasound index; MUI, mixed ultrasound index; GS, grayscale; PD, Power Doppler.

Szkudlarek et al.[11] For this, a scale of 0-3 is used according to the severity of synovial hypertrophy and vascularization.

Recently, a consensus of experts, and with the aim of achieving greater standardization for the conduct of clinical trials, have developed a semiquantitative combined score for synovitis in rheumatoid arthritis that jointly evaluates the degree of synovial hypertrophy and Power Doppler. In this combined score, the severity of synovitis depends on the amount of Power-Doppler signal and the amount and configuration of synovial hypertrophy, quantifying at three degrees (minimal, moderate, or severe synovitis).[13,17]

Main Points

- Ultrasound is a valuable tool for monitoring rheumatoid arthritis.
- The ultrasound indices are necessary to make a correct evaluation of the inflammatory activity in rheumatoid arthritis.
- The use of mixed indices (MUI) will be common in the future in chronic inflammatory arthritis follow-up units.
- In patients in remission, ultrasound predicts well the appearance of inflammatory outbreaks, especially through the use of Power Doppler.
- Regardless of the treatment used, with ultrasound we can show the changes that appear and thus confirm if the treatment is being effective.

Use of Ultrasound as a Metric Tool in Rheumatoid Arthritis

An ultrasound inflammatory index is a tool that allows classifying the degree of joint inflammation at the patient level (evaluating various anatomical locations) at any given time. Ultrasonographic indices have their origin in the first half of the last decade, when several groups of researchers began to develop them. After defining the usefulness of ultrasound to assess inflammatory joint changes in rheumatoid arthritis,[9] the first description of the quantification of joint synovitis in ultrasound evaluation was made by the Szkudlarek group in 2003,[11] defining the degrees of synovitis in grayscale and with Power Doppler. This classification only allowed to quantify the inflammation in the studied joint, without creating any index from it. With it, for the first time, it was possible to have a tool, ultrasound, that allowed classifying the degree of joint inflammation. This way of classifying was accepted and widely used better since its publication. And of course, it has been the basis on which the ultrasound indices have been built. After that, other groups of researchers explored the creation of different indexes based on the study of various joints using a semiquantitative scale.

We can classify the indices into two types: Those that use ultrasound joint evaluation as the only variable and those that, in addition to ultrasound, include other variables. The first could be called simple ultrasound indices (SUI) and the second mixed ultrasound indices (MUI).

The SUI, as we have already commented, include joint evaluation in almost all cases, without considering other inflammatory lesions such as sheath tendon involvement in the anatomical region studied. The latter, MUI, evaluate the patient in a more comprehensive way by including some clinical and laboratory variables. The first to be created were the SUI, and the MUI emerged as an evolution of the first.

The most representative or accepted as SUI by the scientific community have been the reduced index created by Naredo et al.[18] and by Backhaus et al.[19]

In addition to these, many others have been published, all with some characteristics in common, such as the inclusion of the joints of the hands, the evaluation of small joints and some large joint, the bilateral study, and the systematic use of the semiquantitative grayscale and Power Doppler scale. The best known with their characteristics are described in Table 1.

There are three MUI published to date (Table 1), and although their objective is similar, they present several notable differences between them. The first two[20,21] include some variables that can be considered subjective (patient global assessment, quality of life index) and therefore are not too different from a normal clinical index. In contrast, the third[31] does not include any variable that can be considered subjective trying to approach the inflammatory evaluation from a prism less influenced by comorbidities. As with SUI, not

all MUI include, in addition to joint evaluation, the evaluation of the most representative tendons.

One of the great advantages that these instruments confer is the possibility of clearly demonstrating the efficacy of various treatments such as biological therapies, as they have good sensitivity to change. Thus, there are numerous publications where drug efficacy is studied using ultrasound as a measuring instrument. Another possible advantage of the indices is the possibility of evaluating the degree of global inflammatory activity that a patient presents at a given moment of the disease. In this direction, it has been investigated, and first Damjanov et al.[29] and later Salaffi et al.[30] have proposed two MUI indices that allow giving a quantification of the state of inflammatory activity. Both obtain in each evaluation a specific value, identifying if a patient at that moment presents a significant degree of inflammatory activity. Both indices have included clinical and acute phase reactants as variables. Recently, our group has published a new MUI index[31] that, although it may seem similar to the previous ones, has an important difference, the index is built trying to avoid the subjective variables that in fact artifact the clinical indices. In practice, this score seeks to complement the more subjective clinical evaluation with a more objective evaluation of the inflammatory activity.

Most of them included only joints in their development, without considering other structures such as tendons, bones, or ligaments, although these have a relevant role in the clinical manifestations of the disease. Among these indices, there are great structural variability, with important differences in the number of joints included, and therefore in the final quantification range obtained. Some have defined the joints included from a frequency analysis, but in most cases, they have been arbitrarily defined. Furthermore, in only a few, the cutoff values between normality and pathology have been determined.

Despite this, many of them have obtained good result measuring activity or clinical effect of different drugs.

Correlation of Ultrasound Joint Evaluation With Clinical Assessment in Clinical Practice

Clinical indices for the evaluation of RA activity (DAS28, SDAI/CDAI) are useful tools in assessing the response to treatment, although its multiple limitations are well known. The US evaluation of inflammatory activity in RA has a capital value, increasingly recognized in the literature, although its use has not yet been standardized in the main clinical practice guidelines in RA (ACR, EULAR guidelines). This is due, in part, to the fact that multiple studies have indicated the disagreement between both assessments, in clinical trials and in real-life practice. Some algorithms have been proposed that have attempted to locate the best use of US in daily clinical practice and in the optimal evaluation of activity or remission.[32]

A mismatch between the evaluation of activity by clinical indices and by Doppler signal on US of around 20-30% has been reported.[33] Several observational studies have shown that more than a third of patients considered to be in clinical remission according to the DAS28 and the ACR/EULAR definitions still have synovitis on US, and although the prognostic significance of this activity needs to be further evaluated, some authors suggest that we should not talk of true remission without taking ultrasound activity into account.[34] But on the other hand, PD activity can predict the reactivation of the patient with clinical remission criteria and can be useful in the management of treatment reduction or intensification.[35]

In another recent study, DAS28 did not correlate with US outcome measures derived from hands and feet examination.[36] DAS28 did not differentiate between RA patients with subclinical active synovitis versus well-controlled disease on US and 51% of patients had their immunosuppressive treatment optimized. The key result of this study supported the added value of an US examination protocol including hands and feet for optimal diagnosis and management of RA patients with small joint symptoms. The hand with clinically more swollen joints is probably the best choice for monitoring ultrasound activity in clinical practice if a unilateral scoring system is used.[37] Nevertheless, it seems when an ultrasound index including the feet is explored, there is a better agreement with the activity indices than when only the hands are included.[36]

The use of US in clinical practice could improve diagnostic certainty and alter management decisions. In an early arthritis clinic setting, Karim et al.[38] observed that US assessment led to changes in the diagnosis in 53% of patients and in the management plan in 56% of patients. In a study by Naredo et al.[39] conducted in RA patients in sustained clinical remission PD signal at joint level was found predictive of biologic DMARDs tapering failure. At 12 months, 45.5% of the patients presented with a disease flare.

Discrepancies between clinical synovitis and evaluation of subclinical synovitis by US may be different depending on the time of evolution of the disease. It has been observed that subclinical synovitis is long-lasting in RA patients in clinical remission[40] with decreasing frequencies and levels of detectable subclinical inflammation with increasing time in clinical remission. It seems the discrepancies between US findings and clinical findings in the joint examination are more important in long-standing RA and/or fibromyalgia-associated RA patients, where metrics are less reliable.[33] In early RA patients on conventional therapy, PD-positive synovial hypertrophy identified ongoing inflammation, even during remission and predicted a short-term relapse. MRI RAMRIS synovitis score and EULAR-OMERACT US scoring system proved to be sensitive measures of histological synovitis in established RA and early untreated RA in a prospective study.[41]

Another study was designed to assess how potential ultrasound definitions of remission performed in comparison to clinical definitions, the ACR/EULAR Boolean remission was the preferred definition of remission in early RA. The absence of ultrasound inflammation was associated with no radiographic progression.[42]

PD positivity in tendons and joints is an independent risk factor of flare in patients with RA in clinical remission. The STARTER study[43] demonstrated that tendon and joint US can be useful in assessing inflammatory changes in RA in clinical remission to predict disease outcomes.

Swollen joints had both high agreement at patient level and at joint level with US synovitis in a longitudinal observational study.[44] The results of the study support the use of swollen joints in assessments of clinical disease activity while tender joints seemed less reliable for disease activity assessments in patients with established RA. Moreover, either tender or swollen joints might be associated with the presence of coexisting tenosynovitis/peritendinitis[45] and are better detected in the wrist than MCP and PIPs joints, in terms of US agreement with the physical examination. Synovial hypertrophy grade of $\geq$2 in grayscale (GS) becomes the score more reliable to be associated with tenderness and swelling. The latter must be taken into consideration when including US scores either in a multidimensional score or in clinical monitoring, for RA. Considering a score of 1 in GS as nonpathologic findings would help to standardize activity scores and clinical practice reliability among Rheumatologists.[46]

The ARCTIC[27] and TaSER[28] studies showed that monitoring and intervention based on

the evaluation of US activity in patients with recent-onset RA did not have any effect, at least in the short term, in terms of controlling disease activity or in results of progression of structural damage evaluated by radiology or by MRI.[47]

In the ARCTIC study, it was not observed that a tight ultrasound control strategy was superior to the routine clinical control in patients with RA of recent onset. However, it should be taken into account that in the design of this study, patients in clinical control had an intensive visit schedule (13 visits in 2 years), probably superior to which is way off the regular Rheumatologists' patients schedule. Therefore, it is difficult to extrapolate these results to real clinical practice. Patients with intensive ultrasound follow-up received more frequent biological treatment, without obtaining better results in remission rates, which should probably make us consider that therapeutic strategies should be focused on the patient and not on ultrasound. Probably the new multidimensional indexes play an important role in the most comprehensive assessment of the patient. Only one-third of the patients considered in remission by clinical indices would be in remission taking multidimensional activity criteria that include clinical, ultrasound, PROs, and normalization of native T cell populations.[39]

In contrast, in another recent study in the Canadian population—ECHO study—the results support better clinical results and structural damage in patients followed closely with ultrasound control compared to patients in usual clinical follow-up.[48] The ECHO study compared the effectiveness of MSUS to routine care as a disease management tool in patients with moderate-to-severe RA requiring treatment changes due to lack of efficacy. During follow-up, a greater number of RA treatment modifications were applied in the MSUS group compared with routine care, including steroids, nonbiologic DMARDs, and biologic DMARDs. Regarding clinical and patient-reported outcomes, no remarkable differences were observed between groups. However, throughout the study, 50-80% of patients in clinical remission had an MSUS synovitis score of $\geq$1, and 37-73% an erosion score of $\geq$1. In conclusion, the results of this study suggested that MSUS can be useful in the real-world setting for detecting subclinical levels of inflammation and predicting future joint deterioration, thus enabling the tailoring of RA treatment and patient care.

Overall, in the ECHO study, there were no remarkable differences between the two treatment groups regarding achieving standard clinical outcomes, including CDAI/DAS28-ESR remission and LDA. This agrees with the ARCTIC and TaSER studies, which also showed that the use of MSUS was not associated with better clinical outcomes but also not with radiographic outcomes.[27,28]

Utility of Ultrasound in Monitoring Rheumatoid Arthritis Patients

In the last 20 years, several efforts have been done to elucidate if ultrasound is useful in the evaluation of the efficacy of different drugs and if it is a predictive tool in rheumatoid arthritis prognosis.

Ultrasound has been tested as an efficacy evaluation method of different treatments, synthetic and no synthetic drugs. Several studies have proved the capacity of ultrasound as a sensitivity to change tool.[4,12,18,20,29,49–51] Majority of them have demonstrated this goal using classic ultrasound parameters, grayscale, and Power Doppler, but interestingly some have used specific tools (vascular resistance index or IR).[52]

US detect synovitis in patients in clinical remission.[7,34,46,53,54] Indeed, other works have evidenced ultrasound predicts flare in patients in clinical remission,[55,56] particularly Power Doppler but also grayscale[57] probably because residual hypertrophy is not as inactive as could be expected. But this is controversial and needs more effort to confirm. Initially, some studies could not demonstrate the predictive value of PD positivity on flare, but in meta-analysis of Nguyen et al.[58] this question was resolved, and they demonstrated the predictive value of US PD positivity for flare and progressive bone erosion in patients with RA who are in clinical remission. After, in 2016, Han et al. publish a new meta-analysis including more studies confirming PD positivity as a relapse predictor.

Ultrasound predicts progression in patients with subclinical synovitis.[7,56,59] This progression does not appear to be influenced by the duration of remission, disease duration, or medications. The detection of bone erosions also has important diagnostic and prognostic values in patients with early RA.[60–62] Bone erosions are related to inflammatory changes as we know them,[63] and ultrasound gives us a correspondence of this, relating Power Doppler signal in MCP joints and positive bone erosions by ultrasound.[64]

Ultrasound, as above-mentioned, has been tested as a tool in rheumatoid arthritis. It is useful to evaluate inflammatory changes in joints and tendons, gives us relevant information at any time about disease activity at both joint and patient levels. Ultrasound is a useful tool to demonstrate changes with different treatment approaches. And it can improve the evaluation of our patients, especially in those in whom the clinical evaluation is not objective enough. The clinical evaluation and the ultrasound examination are complementary, and neither should replace the other.

Several scores have been created and tested, but any has been accepted as the reference index. Although anyone can be used in research studies and in clinical care if it includes some minimal requirements such as bilateral study, include hands joints and a deeper joint (knee, ankle), and some tendons (wrist extensor tendons, flexor finger tendons, and tibialis posterior). The number of joints necessary is not known yet, but maybe must as maximum as possible. Probably a mixed index will be more useful to identify better the real inflammatory stage and we need to considerer this in next future.

But necessarily, an imaging tool as ultrasonography must be used to monitor disease activity with or without different treatments strategies. But importantly, we need to identify which kind of patients are candidates to use ultrasound, optimizing their utility in our clinical practice.

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