Doppler ultrasonography in rheumatoid arthritis therapy monitoring

Within the last decade, musculoskeletal ultrasonography is playing an increasingly important role in the evaluation and monitoring of patients with chronic inflammatory arthritis. High-resolution musculoskeletal ultrasonography allows direct assessment of intra-articular and periarticular inflammatory activity and structural damage in inflammatory arthritis. There have been a growing number of studies on the criterion and construct validity of ultrasonography with color Doppler or power Doppler techniques for evaluating inflammatory activity in rheumatoid arthritis. Ultrasonography has been proven to be more sensitive and reproducible than clinical evaluation in assessing rheumatoid joint inflammation. Recent studies have demonstrated the responsiveness of grayscale and Doppler parameters in the monitoring of response to therapy in patients with rheumatoid arthritis.

KEYWORDS: Doppler, rheumatoid arthritis, synovitis, therapy monitoring, ultrasonography

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the color Doppler ultrasound technique for imaging studies
- List key components of the pathophysiology of synovial inflammation in rheumatoid arthritis (RA)
- List the features and advantages of high-resolution ultrasonography in patients with RA
- Describe the recommendations for joint imaging in patients with RA

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Musculoskeletal ultrasound basis

Ultrasonography is an imaging modality based on the emission and reception of mechanical sound waves with a frequency greater than the hearing frequency range of the human ear by piezoelectric crystals located inside the transducer or probe. Ultrasound wave frequencies of diagnostic ultrasonography systems range from 3 to 25 MHz. The ultrasonography technique includes B-mode or grayscale imaging of anatomic structures and blood flow detection by the Doppler technique.

Reflection of ultrasound waves through the body tissues depends on their composition, and generates grayscale ultrasonography images in B-mode. Doppler ultrasonography is based on the Doppler effect, which consists of the change of frequency of a sound beam reflected back to the source when it encounters a moving object. The Doppler technique detects the movement of red blood cells in vessels.

The color Doppler (CD) technique is the combination of the Doppler effect and real-time imaging. In CD mode, the information from Doppler technique is integrated in the grayscale image as a color signal. The power Doppler (PD) technique is more recent than conventional CD. PD displays the total integrated Doppler power in color. It increases the sensitivity to detect flow from small vessels and low velocity flow at the microvascular level [1,2].

The greater resolution of anatomic details of superficial musculoskeletal structures offered by high-frequency transducers (7.5–25 MHz) has contributed to high-resolution musculoskeletal ultrasonography becoming an established imaging technique for evaluating periarticular and intra-articular structures involved in musculoskeletal diseases. In addition, the enhanced sensitivity for detecting low-velocity flow in small tendon and synovium vessels achieved by recent CD and PD techniques has led to the incorporation of Doppler ultrasonography in the assessment of periarticular and intra-articular inflammatory lesions.

Ultrasonography is a routinely available, multiplanar, dynamic, noninvasive, portable and relatively inexpensive bedside imaging method with high patient acceptability. This technique facilitates the scanning of all peripheral joints as many times as required at the time of consultation. Musculoskeletal ultrasonography allow an immediate correlation between imaging findings and clinical data, which improves the diagnosis and management of patients with a range of rheumatic diseases from inflammatory arthritis, vasculitis or osteoarthritis, to soft-tissue diseases.

Since ultrasonography is probably the most operator-dependent imaging modality, mainly because of the intrinsic real-time nature of ultrasonography image acquisition, appropriate training and competency assessment for physicians performing musculoskeletal ultrasonography, along with standardized scanning method and criteria for pathology, are highly important to ensure skilled and reliable use of musculoskeletal ultrasonography.

Applications of musculoskeletal ultrasonography in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the development of synovitis, which damages cartilage, bone, ligaments and tendons. Synovial inflammation consists of periarticular vasodilatation followed by synovial proliferation, which is accompanied by angiogenesis resulting in intra-articular blood vessel formation [3]. Hypervascularization and angiogenesis of the synovial membrane are considered to be primary pathogenic mechanisms responsible for the aggressiveness of the rheumatoid pannus on the joint [3].

Assessment of RA inflammatory activity is essential in rheumatologic practice to enable therapeutic decisions and to evaluate disease outcome and response to treatment. Traditionally, the degree of disease activity has been evaluated by measuring subjective clinical variables, laboratory parameters and radiographic findings. Within the last decade, musculoskeletal ultrasonography is playing an increasingly important role in the evaluation and monitoring of patients with chronic inflammatory arthritis, based mainly on the fact that it has a higher sensitivity for detecting synovitis than clinical examination.

High-resolution ultrasonography allows direct assessment of intra-articular and periarticular inflammatory activity and structural damage in inflammatory arthritis, such as joint effusion and synoval hypertrophy, tenosynovitis, synovial and tenosynovial vascularity, tendon and ligament lesions, bone erosions and articular cartilage damage. Several studies have demonstrated that musculoskeletal ultrasonography is accurate for detecting joint effusion and synovial hypertrophy compared with magnetic resonance imaging [4] and direct arthroscopic visualization [5,6]. Ultrasonography has been

proven to be definitely more sensitive and reproducible than clinical evaluation in detecting inflammation in both small and large joints [4,6–12] (FIGURE 1).

Color Doppler and PD ultrasonography techniques detect synovial flow, which is a sign of increased synovial vascularization [13]. The presence of an intra-articular Doppler signal aids in distinguishing active synovitis from inactive intra-articular thickening [13–15] in RA. Within the last decade, there has been an increasing number of studies on the criterion and construct validity of ultrasonography with CD or PD techniques for evaluating inflammatory activity in RA compared with evaluations of histologic features [16–18], magnetic resonance imaging [19,20], clinical and laboratory parameters [7,12] and radiographic outcome [21,22].

Interestingly, recent studies have reported the presence of subclinical synovitis detected by grayscale and PD ultrasonography in a high number of RA patients in clinical remission treated with disease-modifying antirheumatic drugs and anti-TNF agents [23,24]. These results indicate that ultrasonography can contribute to establishing the true RA activity status, in order to optimize the treatment strategy.

Ultrasonography has been shown to be more sensitive than conventional radiography in the detection of bone erosions in target rheumatoid joints, especially in small erosions in early RA [4,25,26]. In addition, ultrasonography is able to detect more erosion progression than radiography [27].

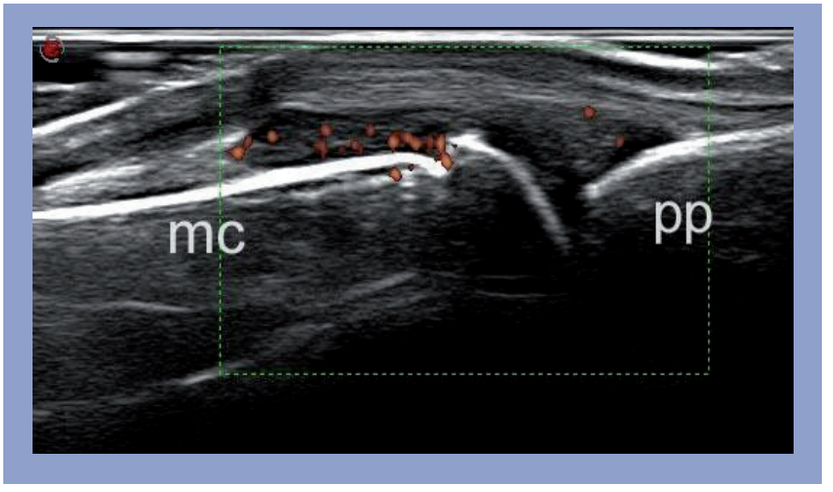

Figure 1. Longitudinal ultrasonographic image of the dorsal aspect of a metacarpophalangeal joint without clinical synovitis shows grayscale synovitis with power Doppler signal.
mc: Metacarpal bone; pp: Proximal phalanx.

Grayscale & Doppler ultrasonography methods for the assessment of synovitis in RA

The Outcome Measures in Rheumatology (OMERACT) group for musculoskeletal ultrasonography has proposed agreed definitions for synovial fluid and synovial hypertrophy [28]. Synovial fluid has been defined as abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal. Synovial hypertrophy has been defined as abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is nondisplaceable and poorly compressible, and which may exhibit Doppler signal.

Synovitis can be detected in different synovial recesses accessible by ultrasonography evaluation in peripheral joints. Several ultrasonography methods for evaluating RA joint inflammation have been described in published studies. Qualitative [6,19], semiquantitative [11,12,16–18,22,29–37] (FIGURE 2) and quantitative scoring systems [7,17,18,20,21,29,38–42] have been used for assessing synovitis by grayscale and/or Doppler ultrasonography in any number of scanned joints ranging from 60 joints [12] to a reduced number of target RA joints, such as wrist, hand or toe joints [7,19–21,29,32,36–39,42]. These variables have made comparison of study results difficult.

A binary scoring of synovitis according to the presence or absence of grayscale synovitis and/or synovial Doppler signal at synovial sites can be

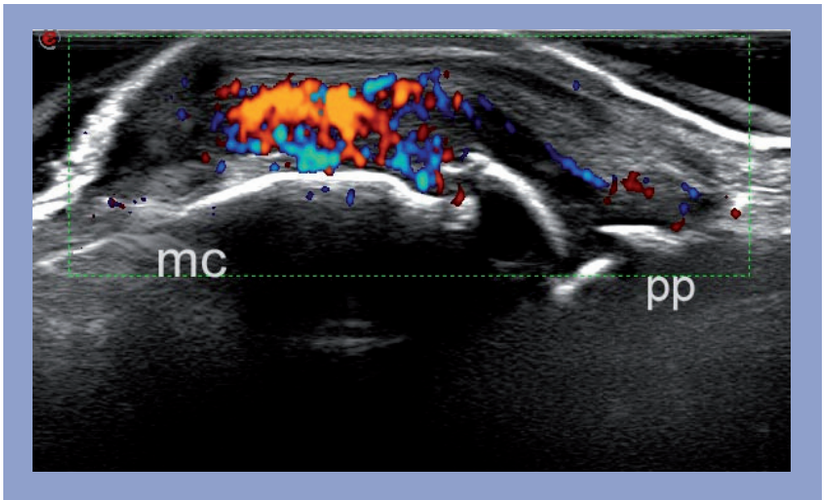

Figure 2. Longitudinal ultrasonographic image of the dorsal aspect of a metacarpophalangeal joint shows marked grayscale synovitis (grade 3) and marked power Doppler signal (grade 3).
mc: Metacarpal bone; pp: Proximal phalanx.

feasible, easy and reproducible, but not sensitive to change. An acceptable to high interobserver and intraobserver reliability for semiquantitative grayscale and PD scoring systems for synovitis has been reported in ultrasonography studies that have assessed reproducibility [12,15,29,30–32,35,37,43]. The EULAR–OMERACT group obtained good interobserver and intermachine reliability from the semiquantitative scoring of synovitis and PD signal in rheumatoid joints [44]. Semiquantitative scoring systems are used by most of the research groups because they are easily applicable in clinical practice, and their findings are available at the time of ultrasonography examination.

Quantitative assessment of synovial thickness or synovial Doppler signal has the advantage of using a continuous variable, which is more sensitive to change than semiquantitative variables. Quantitative Doppler scoring systems include computer-assisted measurement of color pixels in a specific area of interest and spectral Doppler analysis with measurement of the resistance index. Low values of resistance index mean low resistance, indicating inflammation. Both Doppler parameters have been shown to be highly reliable [38,45]. However, they are time-consuming and not feasible in clinical practice. Thus, they are probably more suitable for ultrasonography research.

Doppler ultrasonographic monitoring of response to therapy in RA

In RA, synovial inflammation appears to be the primary abnormality responsible for structural joint damage and functional outcome. There is a relationship between joint inflammatory activity and synovial vascularization. In this case, the monitoring of therapy in patients with RA should focus on measuring joint synovitis. The development of new valid methods for assessing response of synovial inflammation to treatment in RA is a challenge in daily practice and clinical trials, and a relevant research field in rheumatology. At a patient level, any new method for assessment of synovitis should demonstrate construct validity or relation with other measures of disease activity, such as clinical and laboratory parameters. In addition, the tested measurement of disease activity should demonstrate discriminant validity or sensitivity to change, feasibility and an added value over clinical evaluation, such as independent predictive value in outcome measures.

A number of longitudinal studies have demonstrated a significant improvement of joint inflammation evaluated by grayscale and CD or PD ultrasonography in RA patients treated with different drugs, including intra-articular corticosteroid injections, systemic corticosteroid therapy, disease-modifying antirheumatic drugs and biologic agents [14,21,22,29–36,39–43]. Changes in ultrasonography and Doppler parameters were associated with clinical and laboratory response to therapy.

Recent ultrasonography studies [21,29,31–35,39,41,43] have described a significant reduction of joint inflammation in RA as evaluated by grayscale ultrasonography, CD ultrasonography or PD ultrasonography after various durations of treatment with anti-TNF agents, a therapy that has been widely demonstrated to be effective in RA. Most of the earlier studies evaluated small numbers of patients and/or joints and/or had short follow-up periods, which probably limited the ability to investigate the responsiveness of ultrasonography findings. Nevertheless, Ribbens *et al.* [29] and Fiocco *et al.* [31] reported intraobserver coefficients of lower variation than the changes in PD findings. A 28-joint PD ultrasonography assessment has shown responsiveness in 12-month follow-up of early RA patients who were beginning treatment with DMARDs [22], and established RA patients who were beginning anti-TNF therapy [35]. However, in these latter studies, image acquisition variability was not investigated, since intraobserver reproducibility was tested in selected PD ultrasonography images instead of the real-time examination of the joints, which probably introduced bias into the results.

How many joints and what joints should be assessed by ultrasonography and Doppler for overall disease activity monitoring in RA are relevant issues that need to be addressed. A comprehensive ultrasonography assessment, including multiple recesses of all accessible peripheral joints, may be time-consuming for the patient and doctor in daily practice and clinical trials. On the other hand, feasible simplified systems of ultrasonography assessment of joint inflammation should be validated by comparison with comprehensive systems.

Most of the published studies have included a limited number of target rheumatoid joints, and few studies have included tenosynovitis and bursitis as synovial sites assessed by ultrasonography [33,34]. Naredo *et al.* demonstrated construct validity of a global semiquantitative PD ultrasonography assessment from intra-articular and periarticular synovial sites at 28 joints in a large cohort of established RA patients who were starting anti-TNF therapy [35].

Executive summary

Musculoskeletal ultrasound basis

- The ultrasound technique includes B-mode or grayscale imaging of anatomic structures, and blood-flow detection by color Doppler or power Doppler methods.
- High-resolution musculoskeletal ultrasonography has become an established imaging technique for evaluating periarticular and intra-articular structures involved in musculoskeletal diseases.
- Doppler ultrasonography has been incorporated into the assessment of periarticular and intra-articular inflammatory lesions.
- Ultrasonography has many advantages, which can improve the diagnosis and management of patients with rheumatic diseases.
- Ultrasonography is operator-dependent.

Applications of musculoskeletal ultrasonography in rheumatoid arthritis

- High-resolution ultrasonography allows the direct assessment of intra-articular and periarticular inflammatory activity and structural damage in rheumatoid arthritis (RA).
- Several studies have demonstrated that ultrasonography is accurate for detecting joint effusion and synovial hypertrophy.
- Ultrasonography has been proven to be more sensitive than clinical evaluation in detecting inflammation in both small and large joints.
- Various studies have shown criterion and construct validity of ultrasonography with color Doppler or power Doppler techniques for evaluating inflammatory activity in RA.

Grayscale and Doppler ultrasonography methods for the assessment of synovitis in rheumatoid arthritis

- Definitions for synovial fluid and synovial hypertrophy have been proposed by the Outcome Measures in Rheumatology (OMERACT) group for musculoskeletal ultrasound.
- Qualitative, semiquantitative and quantitative grayscale and Doppler methods for evaluating rheumatoid joint inflammation have been used in research studies.
- The EULAR–OMERACT group obtained good interobserver and intermachine reliability from the semiquantitative scoring of synovitis and synovial power Doppler signal in rheumatoid joints.

Doppler ultrasonographic monitoring of response to therapy in rheumatoid arthritis

- A number of longitudinal studies have demonstrated a significant improvement in joint inflammation evaluated by grayscale and Doppler ultrasonography, associated with clinical and laboratory response to therapy in RA patients treated with different drugs.
- How many joints and what joints should be assessed by ultrasonography with Doppler for overall disease activity monitoring in RA are issues that need to be addressed. A comprehensive ultrasonographic assessment including multiple recesses of all accessible peripheral joints may be not feasible in clinical practice.
- A 28-joint power Doppler ultrasonographic assessment has shown responsiveness in 12-month follow-up of early RA patients who were starting treatment with DMARDs and established RA patients who were beginning anti-TNF therapy.
- A recent study showed that a semiquantitative 24-recess, 12-joint power Doppler ultrasonographic assessment of synovitis may be valid, reliable, sensitive to change and feasible for therapy monitoring in established RA.
- Further studies should address the optimal joint count and global ultrasonographic scoring of synovitis in early and established RA.
- Preliminary results may indicate a predictive value of Doppler ultrasonographic findings in RA outcome.

The results of a recent paper showed that a semiquantitative 24-recess, 12-joint PD ultrasonography assessment of synovitis, including bilateral elbow, wrist, knee, ankle and second and third metacarpophalangeal joints, compared with a comprehensive PD ultrasonography assessment of 44 joints, may be valid, reliable, sensitive to change and feasible for therapy monitoring in multicenter longitudinal studies of established RA [43]. Further studies should confirm the optimal joint count and global ultrasonography scoring of synovitis in established and early RA.

There is still a paucity of studies that have investigated the predictive value of ultrasonography and Doppler findings in RA outcomes. Taylor *et al.* evaluated the prognostic value of ultrasonography in RA in a randomized, controlled trial of anti-TNF in early RA [21]. They demonstrated that the baseline synovial vascularization detected by PD in metacarpophalangeal joints correlated with the radiographic joint damage over the following year in patients receiving only methotrexate. Naredo *et al.* reported that the cumulative PD ultrasonography parameters of inflammatory activity in 28 joints over time demonstrated a high correlation with disease activity at 12 months, and stronger correlation with radiographic damage progression after 12 months of DMARD therapy than did the clinical, laboratory and functional parameters, including the Disease Activity Score 28 (DAS28) in patients with early RA [22]. The persistence of synovial PD signal has been shown to have predictive value in relation to radiologic progression in patients with established RA who are treated with anti-TNF agents [35,46].

Conclusion

There is increasing evidence to support the use of ultrasonography with Doppler technique in the assessment of joint inflammatory activity

and therapy monitoring in RA in routine practice and clinical trials. A number of issues need further addressing to demonstrate the impact of ultrasonography on RA outcome, as well as to widely incorporate this technique into RA management. These issues include training and competency of physicians performing musculoskeletal ultrasonography, a standardized scanning method and criteria for pathology, and more data on responsiveness, feasibility and the diagnostic and predictive value of Doppler ultrasonography.

Future perspective

Work is ongoing to address the validity, responsiveness and feasibility of an agreed global Doppler ultrasonographic scoring system for joint inflammatory activity assessment in early and established RA. Future studies will possibly address the diagnostic and prognostic value of ultrasonography with the Doppler technique in RA. Thus, full evidence of the impact of ultrasonography on RA management and outcome will allow the wide use of this technique in both clinical practice and research.

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- **Study on the predictive value of subclinical grayscale and power Doppler US synovitis in structural damage in rheumatoid arthritis joints.**

CME Doppler ultrasonography in rheumatoid arthritis therapy monitoring

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Which of the following most accurately describes the technique of color Doppler (CD) ultrasound?

- ☐ **A** Uses B-mode grayscale imaging
- ☐ **B** Combines Doppler effect and real-time imaging
- ☐ **C** Detects mainly bone structures
- ☐ **D** Uses gamma radiation

2. Which of the following best describes the primary pathogenic mechanism responsible for the aggressiveness of the rheumatoid pannus on the joint?

- ☐ **A** Cartilage erosion
- ☐ **B** Arterial ischemia
- ☐ **C** Fibrosis
- ☐ **D** Hypervascularity

3. Which of the following is an advantage of high-resolution ultrasonography over conventional x-ray or clinical examination in patients with rheumatoid arthritis (RA)?

- ☐ **A** Higher sensitivity for bone erosions
- ☐ **B** More accurate for detecting joint effusion
- ☐ **C** More sensitive for detecting inflammation in small joints
- ☐ **D** All of the above

4. Which of the following represents the minimum number of joints that should be examined by x-ray or ultrasound to assess disease progression in RA?

- ☐ **A** 2
- ☐ **B** 5
- ☐ **C** 8
- ☐ **D** None of the above