Advances in imaging

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Purpose of review
Imaging of inflammatory activity is of increasing importance, and among available modalities, ultrasonography and magnetic resonance imaging (MRI) seem to be of highest impact. The present review includes recent studies describing several aspects of these modalities as well as short descriptions of other promising imaging methods in rheumatoid arthritis (RA).

Recent findings
High reliability has been shown for evaluation of ultrasonography still images. Recently excellent reliability was found when an atlas was used as reference for scoring dynamic images with ultrasonography. The optimal number of joints to examine by ultrasonography for follow-up during therapeutic interventions needs to be further explored. Use of ultrasonographic guidance for injections has showed improved clinical results when compared with blind injections. Ultrasonographic pathology, especially power Doppler, was found to be of predictive value in patients with arthritis. Cartilage damage is an important aspect of structural joint damage in RA, and a reliable assessment system of joint space narrowing has been developed for use with conventional MRI, and various biochemical MRI techniques are being developed to visualize cartilage quality, of which delayed gadolinium-enhanced magnetic resonance imaging of cartilage seems to be the most promising method in RA.

Summary
Novel imaging modalities, especially ultrasonography and MRI, will be of increasing importance to visualize joint inflammation and aid in the diagnosis, treatment and follow-up of patients with RA.

Keywords
imaging, magnetic resonance imaging, rheumatoid arthritis, ultrasonography

INTRODUCTION

Imaging of inflammatory activity is of increasing importance in rheumatology clinical practice, and there is a need for advanced imaging modalities to obtain correct information of the degree of inflammatory activity and to detect early erosive changes. With conventional radiography being the reference method to evaluate structural changes, the two imaging modalities emerging as the most promising are musculoskeletal ultrasonography (MSUS) and magnetic resonance imaging (MRI). MSUS may be performed routinely by the rheumatologist in the clinical setting to obtain information about the amount of synovitis (gray scale) as well as the degree of vascularization, assessed by use of power Doppler [1]. Scanning of joints [2] and soft tissues may give information on synovitis, tenosynovitis, power Doppler activity, effusions, erosions and degenerative changes [1]. The validity of MSUS for assessing synovitis and erosive changes has been shown with MRI and computer tomography (CT) as gold standards [3,4].

Magnetic resonance imaging is a noninvasive tomographic imaging technique that can produce cross-sectional images in any plane, without morphologic distortion or magnification. The projectional superimposition that is a problem with conventional radiography can be avoided with MRI because of its multiplanar capabilities. MRI allows simultaneous examination of all components of the diarthrodial joint, including soft tissues, articular cartilage and bone, without ionizing radiation and adverse effects. Whereas conventional radiography visualizes the structural changes that are a cumulative result of preceding disease activity, MRI allows direct visualization and assessment of

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KEY POINTS

- Both musculoskeletal ultrasonography (MSUS) and MRI are sensitive and reliable tools for assessing inflammation in RA patients.
- High inter-observer concordance for MSUS can be achieved through training and the use of a standard atlas.
- Ultrasonographic guidance significantly improves the performance, clinical outcomes and cost-effectiveness of intra-articular corticosteroid injections in RA.
- There is an increased interest in assessing cartilage damage in RA, and a novel scoring system to evaluate JSN in RA patients by MRI has been developed and may be an important outcome measure in future clinical trials.
- dGEMRIC seems to be the most promising novel MRI technique to assess cartilage quality.
- The place in clinical rheumatology of fusion imaging or other imaging modalities like positron emission tomography and fluorescence optical imaging should be further explored.

synovitis, the primary lesion in RA. MRI is reported to detect RA-erosive change with greater sensitivity than conventional radiography, and to document changes in structural damage over a shorter period of time [5,6]. The present review will focus on recent important studies on MSUS and MRI as well as give some insight into other new and promising imaging modalities.

TEACHING AND PERFORMANCE OF MUSCULOSKELETAL ULTRASONOGRAPHY IN RHEUMATOLOGY

Musculoskeletal ultrasonography is an operator dependent method, and thus it is of major importance to learn the correct technique. Many MSUS courses are available, often including three levels of MSUS experience, described as the most favorable organization of MSUS courses [7]. However, rheumatologists receiving nonmentored training were also shown to achieve diagnostic accuracy in MSUS comparable to highly experienced international experts, whereas reliability was somewhat higher with additional experience [8]. In addition, several studies have shown a steep learning curve for MSUS [9,10].

A recent survey of the routine use of MSUS by rheumatologists in Europe found that in most countries less than 10% of rheumatologists perform MSUS in clinical practice. However, in about one-quarter of the countries, 10–50% of the rheumatologists perform MSUS, whereas only in 10% of all respondent countries did more than 50% of rheumatologists routinely perform MSUS [11▪]. The study describes a huge growth in the routine use of ultrasonography compared with previous surveys, especially in the number of countries that perform MSUS. Taking into account the great interest in the ultrasonography, these numbers are expected to increase substantially during the next few years. A growth in the use of MSUS by rheumatologists was also found in Japan, with doubled use in recent years [12].

MUSCULOSKELETAL ULTRASONOGRAPHY SCORING OF JOINTS

Most studies include a semi-quantitative scoring system (from 0 to 3) of both gray scale and power Doppler. A different number of joints have been included in scoring of RA patients, from 7 to 78 joints [13▪,14], and the different scoring systems have been found to be sensitive to change during follow-up on medical treatment [13▪,14,15]. However, a recent review of scoring systems found it difficult to determine the optimal number of joints to be included in a global ultrasound score [16▪], whereas another study [17] described assessment of both a low and a high number of joints to have a similar sensitivity to change.

RELIABILITY OF MUSCULOSKELETAL ULTRASONOGRAPHY

A systematic review has been performed on the reliability of ultrasonographic detection of gray scale and power Doppler synovitis in RA regarding image acquisition and still-image interpretation [18▪]. A total of 35 studies including 1415 patients were identified. The conclusion was that the intra-observer and inter-observer reliability of still-image interpretation was high, especially for power Doppler, when involving highly trained observers, whereas the reliability of acquisition of MSUS needed to be assessed further. A recent study [19▪] dealt with this question, and by a comprehensive approach including training sessions to achieve consensus on scoring as well as incorporating the use of a reference atlas of representative images of each score for all examined joints, good to excellent reliability was demonstrated for gray scale and power Doppler scoring of a high number of joints in RA patients.

MUSCULOSKELETAL ULTRASONOGRAPHY-GUIDED PROCEDURES

Intra-articular corticosteroid injections are frequently applied in RA patients, and a recent study [20▪▪] examined whether sonographic needle guidance affected the outcomes of intra-articular injection for inflammatory arthritis. A total of 244 joints were randomized for ultrasonographic or palpation-guided injections, and ultrasonographic guidance was found to significantly improve the performance, clinical outcomes and cost-effectiveness. However, in a recent survey of the use of ultrasonography-guided injections in rheumatology, the majority of countries (85%) had less than 10% of rheumatologists routinely performing ultrasonography-guided injections in clinical practice, whereas the remaining countries (15%) reported a rate of 10–50%. The percentage of rheumatologists receiving training in ultrasonography-guided joint injections was below 10% in the majority (72.7%) of countries [21▪].

Sacroiliac joints are difficult to inject by use of palpation, and a MSUS study [22] showed that correct placement in sacroiliac joints was only obtained in 40% of the joints in spite of ultrasonographic guidance. On the contrary, there were no significant differences observed in the clinical outcome between the intra-articular injected group and the periarticular-injected group.

MUSCULOSKELETAL ULTRASONOGRAPHIC ASSESSMENT OF CARTILAGE AND EROSIONS

Cartilage is easily detected by MSUS and several studies have measured the thickness of cartilage to assess the degree of pathology, and a reproducible semi-quantitative scoring system has been described in metacarpophalangeal (MCP) joints of RA patients [23]. However, a recent review [24▪] describes the pitfalls in measuring cartilage thickness, and raises the question of erroneous assessments. The optimal way of measuring cartilage as well as deciding which joints will be best suited for reliable examination should thus be further explored.

The size of bone erosions may be assessed by ultrasonography of bone surfaces available for examination. The validity of ultrasonographic erosions was described with CT being the gold standard [4]. A recent study [25▪] showed that the sensitivity of ultrasonography for detecting bone erosions was high and there was a good correlation between the severity of bone erosions assessed by ultrasonography and micro-CT. However, the specificity of ultrasonography for bone erosions was lower with smaller lesions seen on ultrasonography not always representing breaks in the cortical bone surface. In addition, a follow-up study [26▪] of RA patients on anti-tumor necrosis factor treatment supports the potential of ultrasonography for the assessment of erosive progression, and higher power Doppler and gray scale scores at baseline were detected in the joints with CT progression.

MUSCULOSKELETAL ULTRASONOGRAPHY AS A PREDICTIVE TOOL

A recent study [27▪▪] of RA patients in remission or with low disease activity found that power Doppler signals at baseline could predict relapse or X-ray progression and identify those with adequate disease control. In addition, the presence of synovitis, and especially power Doppler activity, in patients with early nondifferentiated arthritis was predictive of developing RA [28▪]. Another study [29] that addressed the diagnostic utility of MSUS found that in seronegative patients with early inflammatory arthritis, combining power Doppler ultrasonography (PDUS) with routine assessment can have a major impact on the certainty of diagnosis. A study [30▪] of MSUS and MRI in which gray scale synovitis of the wrist was included showed ultrasonographic inflammation to be a predictor of MRI erosive progression in early RA patients.

NEW MUSCULOSKELETAL ULTRASONOGRAPHIC TECHNOLOGY: 3D, FUSION IMAGING AND ELASTOGRAPHY

Three-dimensional (3D) MSUS has been found to have higher reliability than traditional two-dimensional methods [31,32]. However, the place for 3D in clinical rheumatologic practice has not yet been established.

In the future, the fusion of ultrasonography and other imaging methods may be interesting new fields of investigation. MSUS may be fused with MRI or CT, depending on the indication, and thus 3D orientations may be possible for therapeutic or diagnostic interventions [33▪].

Real-time sonoelastography has been used to assess the resistance in several tissues. In rheumatology the method is recently introduced, and few studies have been performed. However, in tissues like the Achilles tendon, it may differentiate between inflamed and normal tendons [34].

CONTRAST-ENHANCED MUSCULOSKELETAL ULTRASONOGRAPHY

Contrast-enhanced ultrasonography (CEUS) has been explored for the vascularization of tenosynovitis, and found to have significantly higher

sensitivity than PDUS by improved detection of intra and peritendinous vascularity [35▪]. In addition, CEUS has a higher sensitivity compared with color Doppler ultrasound in the identification of abnormal vascularization in joint inflammation [36]. The exact measurement of active synovitis and the analysis of time-intensity curves allow a quantitative assessment of inflammation, which is important for staging and follow-up work. However, its place and benefits in arthritis management are not yet clearly established and the method should be standardized, and its diagnostic and prognostic value as well as utility in monitoring therapy should be verified in subsequent studies.

POSITRON EMISSION TOMOGRAPHY IMAGING

[(18) F] fluorodeoxyglucose (FDG) is a tracer for glucose metabolism. Its distribution is observed in inflammatory tissue, including macrophages, capillaries, and fibroblasts. RA is characterized by fibrovascular proliferation and causes high FDG uptake. The method enables detailed evaluation of disease in large joints throughout the whole body. Several clinical studies of RA have demonstrated that FDG uptake in affected joints reflects the disease activity, and FDG positron emission tomography (PET) has been shown to detect and monitor the response to therapy [37]. In addition, subclinical arthritis in anticitrullinated protein antibody (ACPA)-positive arthralgia patients could be visualized by (R)-[(11) C]PK11195 PET and was associated with development of arthritis within 2 years of follow-up [38▪]. Another study [39] reported the first true hybrid PET-MRI examination of the hand in early RA exploiting the advantages of combining both modalities. Increased 18F-FDG uptake was present in synovitis and tenosynovitis as identified on contrast-enhanced MRI, and the authors conclude that in RA, true hybrid 18F-FDG PET-MRI of the hand is technically feasible and bears the potential to directly visualize inflammation. However, the possible contribution of FDG PET to the management of patients with RA remains to be investigated.

FLUORESCENCE OPTICAL IMAGING

Indocyanine green (ICG)-enhanced fluorescence optical imaging (FOI) is a new technology offering sensitive imaging detection of inflammatory changes in patients with arthritis. In a recent study of patients with arthritis in the hand [40▪▪], FOI was more sensitive than clinical examination and showed good agreement with clinical examination, PDUS and MRI, while showing more positive results than these. For the detection of synovitis and tenosynovitis, FOI seemed to be as informative as 1.5 T MRI and ultrasonography. However, this was the first study using FOI in humans, and the advantages of this imaging modality should be studied further, and especially the specificity regarding detection of synovitis needs to be established.

DIAGNOSTIC AND PROGNOSTIC USE OF MAGNETIC RESONANCE IMAGING

A recent review by Suter *et al.* [41▪] systematically evaluated the diagnostic and prognostic capability of MRI in patients with undifferentiated inflammatory arthritis or early RA. Eleven diagnostic studies included 606 patients with undifferentiated inflammatory arthritis. The sensitivity of MRI for diagnosing RA ranged widely, from 20 to 100%, as did the specificity (from 0 to 100%). Seventeen studies involving 710 patients investigated the prognostic value of MRI, but the methodology had variable quality. MRI findings were significantly associated with subsequent radiographic progression in only two of the nine studies that used uniform treatment throughout. They concluded that data evaluating MRI for the diagnosis and prognosis of early RA are currently inadequate to justify widespread use of this technology for these purposes, although MRI bone edema may be predictive of progression in certain RA populations.

A recent article that was not part of the review by Suter *et al.* was recently published [42▪], looking into MRI as a tool for early diagnosis of RA in patients with undifferentiated inflammatory arthritis. The study included 116 patients, of which 27 developed RA. A prediction model was developed, and its performance was tested and compared with that of a previous model developed by van der Helm-van Mil *et al.* [43] (the vdHvM model). This previously validated clinical prediction model included nine variables: sex, age, localization of symptoms, morning stiffness, the tender joint count, the swollen joint count, the C-reactive protein level, rheumatoid factor positivity, and the presence of anticyclic citrullinated peptide antibodies [44]. In the novel model MRI features of bone marrow edema (BME) in the metatarsophalangeal and wrist joints are included, and the outcome of RA or non-RA was correctly identified in 82% of the patients with the novel model, compared with 60% with the vdHvM model.

MAGNETIC RESONANCE IMAGING EVALUATION OF INFLAMMATION

In RA, conventional postcontrast MRI of the wrist and MCP joints can be used to assess joint

inflammation, and the reference method for assessing the degree of inflammation has been the OMERACT RA MRI Scoring (RAMRIS) system [45], which has been shown to be reproducible and sensitive to change [46,47]. However, the use of this system in clinical practice is limited by the long time needed to perform the scoring. In a recent study [48▪], the correlation between assessment of inflammation using dynamic contrast-enhanced MRI (DCE-MRI) analyzed by a novel computer-aided approach and the semi-quantitative scores of synovitis and BME by the RAMRIS system were assessed in the wrists of patients with RA. They showed that the computer-aided analysis of DCE-MRI data significantly correlated with RAMRIS synovitis and BME and was twice as fast to perform. This technique is promising for quick semi-automated assessment of joint inflammation, but needs further validation.

MAGNETIC RESONANCE IMAGING EVALUATION OF CARTILAGE AND JOINT SPACE NARROWING

Magnetic resonance imaging is frequently used as an outcome measure in RA clinical trials, utilizing the OMERACT RAMRIS score [45], evaluating bone erosions, BME, and synovitis. Evaluation of joint space narrowing (JSN) was omitted in the early phase of developing the RAMRIS during the late 1990s, because the quality of MR images at that time was insufficient to evaluate cartilage thickness. However, MR images with higher signal and resolution are now available. Cartilage damage is an important aspect of structural joint damage in RA, and a reliable MRI assessment system of JSN, reflecting cartilage loss, would further improve the usefulness of MRI in measuring outcome in RA clinical trials. Thus, the same group that developed the RAMRIS has now developed a preliminary MRI scoring system of JSN in RA that showed construct validity and good intra-reader and inter-reader agreements, and may prove to be a useful outcome measure in RA [49▪].

Various biochemical MRI techniques [such as T2$*$ mapping, native T1 mapping, ΔR1 and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC)] have been developed to assess the properties of normal and pathological cartilage. These noninvasive measures of cartilage quality may have the potential to detect cartilage damage before irreversible volume loss occurs. In a recent study [50▪] these novel MRI techniques sensitive to molecular cartilage damage were evaluated in RA patients and healthy controls. They conclude that their results support the use of postcontrast dGEMRIC for the assessment of MCP joint cartilage quality in RA. In another study [51▪], dGEMRIC was able to show that cartilage damage was present in MCP joints of disease-modifying antirheumatic drug(s)-naive patients with early RA, despite the absence of JSN on standard radiography and MRI. So far, dGEMRIC seems to be the most promising MRI technique to assess cartilage damage in RA patients, but further studies are needed to compare the different techniques and the clinical importance of the findings.

CONCLUSION

It is important for rheumatologists to have correct information about the degree of inflammatory activity as a basis for diagnostic and therapeutic decisions. MSUS is an imaging method for detecting synovitis during the clinical examination, and the method has been shown to be valid, reliable and sensitive to change. In addition, MSUS may be used to explore erosions and secondary degenerative changes in RA patients.

Magnetic resonance imaging is a sensitive modality that can assess both inflammatory and structural lesions. The exact diagnostic and prognostic value of this modality is still under question, and current evidence is at present inadequate to justify widespread use of this technology for these purposes, although some studies have shown that BME may be predictive of progression in certain RA populations, and that diagnostic algorithms including MRI features improve the diagnostic accuracy in undifferentiated inflammatory arthritis compared with existing algorithms. New imaging modalities and techniques may be useful to assess inflammatory activity in RA, but further studies must explore their clinical value and place in the examination and follow-up of RA patients.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 345–346).

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