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TITLE PAGE

Title: Magnetic resonance imaging and ultrasound in rheumatoid arthritis

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Abstract

Purpose of review

To overview the recent literature on the use of magnetic resonance imaging (MRI) and musculoskeletal ultrasonography (MSUS) in rheumatoid arthritis (RA).

Recent findings

Subclinical inflammation has been widely confirmed, even in the earliest phases of RA. The presence of osteitis has added benefits to modern diagnostic criteria, and ACPA positive patients have demonstrated higher osteitis scores. A model for prediction of RA onset employing usual clinical data and power Doppler (PDUS) has been reported. The presence of tenosynovitis may also be an early finding in RA. Modern imaging continues to inform our concept of pathogenesis with reports on the direct relationship of synovitis to cartilage proteoglycan loss using compositional MRI measures. Growing data on the validity of MRI as an important predictor of clinical and radiographic damage endpoints has been reported and reflected in the growing use of this outcome in many contemporary biologic therapy trials. Much work has been presented on improved and validated MSUS scores with reduced and feasible joint counts. The role of US in making sensible decisions when monitoring biologic use, and in tapering, has been reported.

Summary

The recent literature demonstrates improved validity and utility for both MRI and MSUS in diagnosis, prognosis and monitoring of RA.

Introduction

Modern imaging has come of age as a robust biomarker for rheumatoid arthritis (RA). The American College of Rheumatology (ACR) Clinical Trials Task Force Subcommittee on Imaging has presented the extensive validation for MRI in randomized control trials. [1] Musculoskeletal ultrasonography (MSUS) has established its role in many rheumatology clinics and training curriculae. [2] High resolution gray scale US (GSUS) and power Doppler US (PDUS) assist the diagnostic performance of 2010 ACR/EULAR classification criteria in early detection of RA. [3] In this review we focus on recent publications on the utility of MRI and MSUS in RA diagnosis, pathogenesis, clinical trials and routine clinical practice.

MRI and diagnosis of RA

A recent European League Against Rheumatism (EULAR) task force has highlighted the importance of MRI as a sensitive diagnostic tool in doubtful clinical scenarios, as well as a specific predictor of treatment response in RA. [4] Krabben et al examined 179 patients with early arthritis, performing a 68 tender and 66 swollen joint count, followed by extremity 1.5T MRI of metacarpophalangeal (MCP) joints, wrist and metatarsophalangeal (MTP) joints. Synovitis and tenosynovitis at MCP and wrist joints were independently associated with clinical swelling. MRI could detect inflammation in 54-64% of joints with no clinical swelling. [5]

Van Steenbergen et al examined a cohort with clinically suspected arthralgia (CSA). MRI inflammation (combined osteitis, synovitis and tenosynovitis score ≥3) was

present in 44% of 93 patients; 35% of 29 patients with MRI inflammation who were followed up progressed to overt arthritis within 4 months. [6*] In an early arthritis cohort, Stomp et al noted numerically higher scores for synovitis, tenosynovitis and osteitis in RA as compared to other arthropathies, though the MRI score in RA was not statistically different from other arthritides. [7] Anti-citrullinated peptide antibody (ACPA) positive patients showed significantly higher scores for osteitis.

That MRI findings alone are not diagnostic of RA is not surprising. Tamai et al studied 166 patients with undifferentiated arthritis; patients fulfilling the 1987 ACR criteria for RA at 1 year or those who were on disease modifying anti-rheumatic drugs (DMARDs) within the first year of symptoms were the reference standard. Osteitis was the most useful feature with a positive predictive value of 84.9%, followed by bone erosion (81%) and synovitis (72%). A decision tree algorithm, which involved applying the 2010 criteria followed by MRI-detected osteitis identified RA better than the 2010 RA classification criteria alone. [8]

The importance of tenosynovitis in early RA is a recent emerging theme. Nieuwenhuis and colleagues performed MRI of the MCPs and wrist in 178 early arthritis patients. Tenosynovitis was present in 65% of the total cohort and significantly higher in RA patients than those without RA (75% vs 59%; p=0.023). Flexor tenosynovitis at MCPJ5 and extensor tenosynovitis at MCPJ2, MCPJ4 and wrists showed greater levels of tenosynovitis in the RA patients, independent of

joint synovitis. There was no association of ACPA seropositivity with tenosynovitis. [9]

MRI and pathogenesis in RA

Conflicting reports exist on the relationship between obesity and RA progression. Baker et al examined data from two large clinical trials. Radiographic progression at 52 weeks was significantly lower in the obese/overweight category compared to those with low/normal weight ($p=0.002$). Osteitis scores were also significantly higher in patients with low/normal BMI. [10] The pathogenic implications of these findings are unknown.

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2 mapping are techniques used to detect cartilage proteoglycan loss before macroscopic morphological deformity. [11] Herz et al applied dGEMRIC and T2 mapping to cartilage in finger joints and compared extent of synovitis, osteitis and bone erosions with cartilage microstructure. [12*] While bone erosions did not have any association, synovitis and osteitis were related to cartilage damage. Schleich et al looked for possible association between severity of RAMRIS synovitis and cartilage composition, assessed by dGEMRIC of MCPJs in RA patients. This study also showed a significant association between cartilage loss and severity of synovitis. [13]

Rowbotham et al reported the novel feature of interosseous tendons tenosynovitis (47.7% of 44 patients studied), seen more often adjacent to MCP joints with

synovitis than those without ($p<0.001$); it was also more common in those with flexor tenosynovitis compared to those without ($p<0.001$). [14] Siddle et al showed increased number of erosions on the proximal and plantar aspects of the MTP joints in RA, suggesting that erosions (in these locations) may be mechanically driven. [15]

MRI and RA in clinical practice

The discrepancy between true imaging-detected inflammation and clinical findings means MRI might improve our clinical tools. Baker et al developed modified common composite disease activity scores using MRI inflammation as the standard, and validated the scores in a second large cohort. The modified scores had better predictive value for radiographic progression than the existing activity measures. [16]

Developing biomarkers that will predict clinical response to a given therapy remains a holy grail for the field. Maclsaac et al, in a randomized, controlled trial of infliximab with methotrexate versus placebo with methotrexate, demonstrated different patterns of pre-treatment gene expression in whole blood from dynamic contrast enhanced MRI responders and non-responders. [17]

MRI and clinical trials in RA

Data from a randomised trial involving 256 methotrexate-naïve RA patients, imaged with conventional radiographs and MRI at multiple time points, demonstrated that high baseline synovitis and osteitis, increase in RAMRIS erosion score at weeks 12

and 24, and poor response to therapy at week 24, were independent predictors of radiographic progression at 12 months. [18] In a separate analysis based on large RCT data, this group also reported requirements for substantial reduction of sample size and study duration if MRI is used as the primary end point in clinical trials (Figure 1). This study also demonstrated that early MRI progression of damage scores positively correlated with 2-year HAQ scores. [19**]

MRI has been used extensively as an outcome tool in assessing biologics. Peterfy et al utilized MRI in a RCT where bone erosion progression and cartilage loss (measured using a novel semi-quantitative score) were reduced significantly in the rituximab (RTX) groups. [20*] In a phase II MRI sub-study involving apremilast, there were no significant changes in the inflammation measures (synovitis and osteitis) at week 16 for 2 doses of apremilast (20mg and 30mg). However around 80% of patients receiving apremilast did not show any worsening of erosions or joint space narrowing. [21] Ostergaard et al used multiple MRI time points in 41 patients with established RA treated with certolizumab for 16 weeks, followed by a 24-week open-label extension. Significant reduction in synovitis and osteitis scores was observed at week 16. This study provided information about the timing of early MRI endpoints for subsequent studies. [22] MRI was also used to assess a treat-to-target strategy with methotrexate, intra-articular steroid plus adalimumab/placebo in early RA patients. Adding adalimumab had an additive effect in suppressing osteitis and tenosynovitis at 1 year. [23]

More recently another study explored the effects of tofacitinib alone or in combination with MTX versus MTX alone on a range of MRI endpoints including a novel automated method quantifying RAMRIS components (using active appearance modelling, called RAMRIQ) and compared this with RAMRIS and dynamic quantitative MRI. RAMRIQ was found to be more responsive in measuring outcomes, with significant differences in favour of both tofacitinib groups. [24]

New MRI scoring systems

Forefoot bursae (FFB) are associated with RA disease activity and predict foot disability. Cherry et al devised a novel MRI-based score for evaluation of FFBs in patients with RA, which was shown to have moderate to substantial reliability. [25] Axelsen et al investigated the ability of whole body MRI (WBMRI) in RA to detect inflammation and structural damage. Synovitis and osteitis by WBMRI were noted more frequently than clinical findings. WBMRI also determined (infrequent) enthesitis in patients with RA. This technology may underpin feasible systems to assess 'total body' inflammation and MRI 'joint counts'. [26]

MRI in determining remission

Ranganath et al, in a sub-study to the Treatment of Early Aggressive Rheumatoid arthritis (TEAR) trial, assessed MRI findings across different clinical remission criteria in a seropositive early RA cohort over 2 years. Though total MRI inflammatory scores were lower during clinical remission, none of the patients had

a score of zero for any variable at the end of study, supporting previous evidence on persistent subclinical disease in clinically apparent remission. [27]

MSUS and diagnosis of RA

A phase of pre-clinical RA, with rising titres of ACPA is now well recognized up to 2 years prior to disease onset. [28] A UK group studied 100 consecutive patients with new non-specific musculoskeletal symptoms and positive ACPA. Half the patients progressed to inflammatory arthritis, mostly within the first 12 months. They devised a model for progression to inflammatory arthritis (IA), with 3 of four variables (tenderness of hand or foot joints, early morning stiffness ≥30 min, high-positive autoantibodies and positive PDUS) strongly associated with IA outcome. [29**]

There is scarcity of data on the specificity of erosions in RA diagnosis. Zayat et al. examined the incident rate ratios of joints with erosions in RA, psoriatic arthritis, gout and osteoarthritis patients: they were 2.50, 2.28 and 5.41, respectively. Presence of any joint with extensive erosive damage was specific for RA (89.2%) but not very sensitive (50%). Large erosions in the 2nd and 5th MCPJ, 5th MTPJ and distal ulna were highly specific (97.9%) but moderately sensitive (41.4%) for RA. The authors observed a diameter of ≥1.5mm achieved the best trade-off between sensitivity and specificity for RA diagnosis. [30]

Minowa et al studied 122 treatment-naïve undifferentiated arthritis patients with MSUS and laboratory findings. MSUS evaluation was performed on proximal interphalangeal (PIP), MCPJs and both wrists. During follow up, the diagnosis of RA was defined by the attending physician. In seropositive RA, the ACR/EULAR classification criteria (OR=15.53) and PD ≥ 2 for ≥ 1 joint (OR=10.48) were the contributing factors, while only the latter variable contributed (OR=20.00) in sero-negative patients. [31]

MSUS and pathogenesis in RA

An Italian group has reported a strong correlation of GSUS and PDUS in twelve treatment naïve early RA patients with pro-angiogenic and lymphangiogenic gene expression profiles. [32] Another study on 177 RA patients compared synovial histology (from 215 joints undergoing synovectomy and reconstructive surgery) with MSUS. PD signal grade reflected the histological scores in both large and small joints and also correlated well with DAS28, C-reactive protein and matrix metalloproteinase-3. [33]

Alsuwaidi et al performed high resolution MSUS, including PDUS of ankle joints in 80 patients of RA with a mean DAS28 score of 5.0. Tibiotalar and talonavicular joints were observed to have the most synovitis in both symptomatic and asymptomatic patients. Half the asymptomatic joints showed signs of synovitis on scanning. However, PDUS activity was seen predominantly in symptomatic patients. [34*]

Sreerangaiah et al studied 85 ACPA positive, biologic-naive RA patients. GSUS and PDUS of 10 MCPJs were performed at 0 and 12 months. 3D PD had the strongest bivariate association with changes in vdHS score ($R^2 = 0.34$) and MSUS erosion score ($R^2 = 0.38$). [35*]

MSUS and RA in clinical practice

The randomized Targeting Synovitis in Early RA (TASER) study investigated the utility of MSUS in improving the accuracy of disease activity assessments. MSUS identified persistent disease activity in a quarter of patients with low disease activity or clinical remission and led to modified therapeutic decisions in 29% of assessments. On the flip side, in 67% assessments, MSUS did not identify active disease in the moderate disease activity but minimal clinical synovitis group, preventing treatment escalation. [36]

The optimal time point for repeat rituximab (RTX) in RA has not been clearly defined. Reiche et al evaluated MSUS changes in 20 longstanding RA patients with moderate to high disease activity (mean DAS28 5.3±1.0) on RTX, and compared the findings with clinical and laboratory data. [37] A 7-joint (wrist, MCP/PIP joints 2 and 3, and MTP joints 2/5) GS and PDUS score (US7) was calculated for synovitis, tenosynovitis and GSUS for erosions. [38] PDUS was a better score to decide on RTX re-therapy as it detected onset of disease activity before worsening of clinical symptoms.

Another recent theme in imaging has been its ability to enable tapering or withdrawal of biologics. Naredo et al investigated the predictive value of PDUS detected synovitis for predicting failed biologic therapy at 6 and 12 months in 77 RA patients in sustained clinical remission. Within 12 months 14 (30.4%) patients on subcutaneous biologics and 21 (67.7%) patients on intravenous biologics developed tapering failure. Baseline DAS28 and high global score of PDUS synovitis were the independent predictors of biologic therapy failure. [39*]

MSUS and clinical trials in RA

The short-term PDUS response to anti-TNFα therapy in six target joints (second MCP, wrist and knee bilaterally) was monitored in 68 RA patients. There was significant decrease in the joint score at all articular sites, and a moderate significant positive correlation between the global PDUS score and change in DAS28 at 3 months. [40]

The APPRAISE study assessed the capability of a composite PDUS score (improvement in the global OMERACT-EULAR synovitis score of bilateral MCP 2-5) to measure early effect and time to response to abatacept in 104 biologic-naïve RA patients who were MTX inadequate responders. Both composite PDUS score and PD signal showed statistically significant reductions in individual joint synovitis by week 1. There was a continuous improvement in the global score (MCP 2-5) as well as each of the component scores till 24 weeks. The authors proposed a novel nine-paired joint set (shoulder, elbow, wrist, MCP 1, MCP4, proximal interphalangeal

joint – PIP 2, knee, MTP 3 and MTP 5) which worked as well as a 22-paired joint set for disease activity monitoring. [41**]

New MSUS scoring systems

There remains no standard guideline on the number of joints to be used for monitoring RA. Several studies above have proposed and validated semi-quantitative simplified scoring systems examining limited number of joints. [29,38,41,42] Yoshimi et al retrospectively analysed 234 patients with RA to establish the optimal number and combination of joints to be assessed by PDUS in daily practice. Of the 28 joints in DAS28, 24 were scanned and a semi-quantitative scale of 0-3 was used to score PD signal in each joint. An 8-joint (bilateral wrist, knee, MCP 2,3) PDUS synovitis assessment correlated well with the total PD score-24 (r_s = 0.97, $p<0.01$), with sensitivity and negative predictive value of 98.1% and 96.2%, respectively. [43]

Aga et al compared the MSUS severity and distribution of joint inflammation in 227 patients with treatment naïve early RA and 212 patients with established disease, to develop and validate a feasible MSUS inflammation score. Two candidate sets were identified, 7 joints/2 tendons and 9 joints/2 tendons, with the latter retaining 93% and 92% of information in the total GSUS and PDUS scores. [44] Tan et al, in a pilot study showed the efficacy of novel individualized MSUS and individualized composite ultrasound joint-selection methods (based on symptomatic joints) in

demonstrating inflammatory improvement in RA, when compared to existing methods. [45]

Mandl et al compared MSUS measures with anatomical measurements of metacarpal cartilage thickness (MCT) in cadaveric specimens. There was no significant difference between MCT measured by anatomical or ultrasound method. A positive linear relationship between anatomical and ultrasound MCT was observed. The relationship between MSUS-measured MCT and radiographic joint space narrowing (JSN) demonstrated moderate agreement (0.6; 95% CI 0.23 – 0.83). [46]

MSUS in determining remission

Gartner et al studied the decrease of subclinical signs of disease activity in RA patients who had sustained clinical remission (clinical disease activity index ≤2.8) using MSUS of 22 joints of both hands. Joints showing higher GS signals had significantly shorter time (2.2±2.4 years for GS3, $p < 0.001$) since last clinical swelling and positive MSUS assessments as compared to those with lower GS signals. A similar trend was seen with PD signals too. [47*]

Fukae et al studied RA patients with sustained clinical low disease activity using PDUS to measure quantitative synovial vascularity (SV). MCP plus PIP joints with positive SV had significantly higher changes of TSS ($p < 0.0001$) and joint space narrowing score ($p < 0.0001$) compared to those with negative SV. [48]

Conclusion

MRI and US are finding increasing utility in RA both in research, where imaging will mean smaller and shorter duration clinical trials, and in clinical practice. Future research to optimize the role of MRI and US in management of RA must address recommendations for specific joints to be assessed for both diagnosis and monitoring, and support the role of imaging in cost-effective clinical management algorithms. Improving technology and quantification will continue to evolve the usefulness of modern imaging.

KEY POINTS

- MRI and US are highly sensitive modalities and their use can improve diagnostic criteria for RA
- The concept of subclinical inflammation has been established by MRI and US, and is evident from the earliest phases of RA to those with sustained clinical remission
- MRI studies of cartilage composition have confirmed a close relationship between synovitis to cartilage proteoglycan loss
- As evidence on the predictive validity of early MRI findings for radiographic progression and functional outcomes accumulates, MRI is increasingly being employed in outcome assessment in RA therapy trials
- Reduced US joint scores are being developed and validated to improve feasibility of both diagnosis and monitoring in routine clinical care

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Conflicts of interest

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