Rheumatology 2008;47:13–21
Advance Access publication 28 November 2007
doi:10.1093/rheumatology/kem250

Review

MRI of rheumatoid arthritis—image quantitation for the assessment of disease activity, progression and response to therapy

R. J. Hodgson[1,2], P. O'Connor[2] and R. Moots[3]

Magnetic resonance imaging (MRI) allows the direct visualization of many bone and soft tissue changes in rheumatoid arthritis. Synovitis volume, bone marrow oedema and bone erosions are suitable for serial measurement. The outcome measures in rheumatoid arthritis clinical trials (OMERACT) rheumatoid arthritis magnetic resonance imaging (RAMRIS) system is designed to allow straightforward, reproducible scoring of all these features. Alternatively, synovial volumes may be directly and quickly measured using semi-automated techniques. There is the potential for similar systems for measuring erosions. Dynamic contrast enhanced MRI depends on the rate of enhancement of the synovium after intravenous contrast agent. Measurements depend on the underlying physiology of the inflamed synovium, in particular the vascularity and capillary permeability which are expected to closely mirror inflammatory activity in the joint. Measurements from MRI have been shown to correlate with clinical, laboratory, imaging and histological measures of inflammation, predict erosive progression and respond rapidly to various types of treatment. They are, therefore, expected to be good measures of disease activity, progression and response to therapy.

Key words: MRI, Dynamic contrast enhanced MRI, Image analysis, Rheumatoid arthritis.

Introduction

Imaging techniques have played an important role in assessing disease progression and response to treatment in rheumatoid arthritis (RA) for many years [1]. Plain X-rays have been widely used together with scoring systems designed to quantify disease and measure progression and response to treatment [2]. However, these rely on relatively late disease features such as bone erosion and joint space narrowing.

Magnetic resonance imaging (MRI) can directly visualize the bone and soft tissues in three dimensions, and has the potential to measure inflammatory activity and joint destruction. Ultrasound, bone scintigraphy and positron emission tomography (PET) are also sensitive techniques for assessing RA, and the relative roles of the different imaging modalities have yet to be established. Ultrasound can rapidly assess multiple joints and is well established in the clinical assessment of synovitis and tenosynovitis, although it is less sensitive than MRI for detecting erosions and cannot assess marrow oedema [3]. Doppler imaging provides information on disease activity. Reproducible quantitation is difficult due to the operator dependence of the technique, however, recent 3D systems may overcome this limitation [4]. Bone scintigraphy can assess the whole body, although the specificity is relatively low and MRI is more sensitive for detecting erosions [3]. F-18 fluro-2-deoxyglucose (^{18}FDG)-PET provides unique information about metabolic activity and is inherently quantitative [5]. Its sensitivity for detecting joint inflammation and response to treatment relative to MRI is yet to be determined.

In this article, we review the MRI quantitation of synovitis, bone marrow oedema and bone erosions using scoring systems, direct volume measurement and dynamic contrast enhanced MRI. For each system we discuss suitable MRI protocols, measurement techniques and reproducibility. Discussion of scoring systems will be limited to the widely accepted RA MRI Scoring (RAMRIS) technique. Direct volume measurements and dynamic contrast enhanced MRI are less mature and an overview of the different techniques is included. These quantitative techniques are rarely used in routine clinical practice at the present time, but they have been applied to clinical trials, the results of which are summarized here.

Scoring systems

The Outcome Measures in RA Clinical Trials (OMERACT) group have devised and tested a RAMRIS system for the wrist and MCP joints. This aims to provide a well-defined, reproducible measurement system suitable for multi-centre use [6]. Of the various measurements considered, bone erosions, bone marrow oedema and synovitis volume provided acceptable reproducibility [7].

OMERACT defines a core set of MR sequences [8]. T1-weighted images acquired before and after the administration of gadolinium-based, intravenous contrast are required to demonstrate enhancing synovitis. These images are also helpful for identifying cortical defects, a defining characteristic of bone erosions. Erosions must be visible in two planes to meet the RAMRIS criteria, hence axial and coronal images are recommended. Small erosions need images from thin slices for reliable visualization and the OMERACT studies used slice thickness of 3 mm [7, 9, 10]. Bone marrow oedema is best assessed on pre-contrast fat-suppressed T2-weighted images, typically in the coronal plane. Figure 1 shows examples of synovitis, erosions and marrow oedema on T1-weighted post-contrast images. Studies looking at low-field (0.2 T) MR systems for OMERACT scoring have shown good correlation with standard field systems (1.5 T) for scoring synovitis and erosions but not marrow oedema [11, 12]. Contrast dose affects the synovitis scores [13], hence a standard dose of 0.1 mmol/kg is usually used [7, 9, 10]. Although the RAMRIS system is specific to the wrist and MCP joints, it has been modified for use in the feet, and there is some evidence to suggest that, as with X-rays [14], MRI of the feet may be more sensitive, revealing changes in the feet even if the hands are not involved [15]. Scoring of the feet may therefore be of use in early disease.

The score for each of synovitis, bone erosions and bone marrow oedema is made up from the sum of scores from individual joints. Synovitis is scored 0–3 in each of the distal radioulnar, radiocarpal, intercarpal-carpometacarpal and 2nd–5th MCP joints.

[1]MARIARC, University of Liverpool, Liverpool, [2]Chapel Allerton Hospital, Leeds and [3]Clinical Rheumatology, School of Clinical Sciences, University of Liverpool, Liverpool, UK.

Submitted 2 May 2007; revised version accepted 8 August 2007.

Correspondence to: R. Hodgson, MARIARC, Pembroke Place, Liverpool L69 3GE, UK. E-mail: RichardHodgson@btinternet.com

Bone changes are scored in each of the carpal bones, distal radius, distal ulna and metacarpal bases. Erosions are scored 0–10 and oedema 0–3 as a fraction of the bone involved within 1 cm of the joint line.

The reliability of the OMERACT scoring system has been assessed in several studies and shows low intra-reader variation (interclass correlation coefficient, ICC > 0.9) [16]. The results for inter-reader correlation are less good with substantial variation between studies for synovitis (ICC 0.58–0.78), erosions (ICC 0.3–0.83) and oedema (ICC 0.32–0.95) [7, 9, 16, 17]. This variation may in part reflect the different characteristics of the patients groups studied [9]. There is also controversy over the relative reliability of wrist and MCP scores [7, 9, 18]. Studies looking at changes in OMERACT scores have shown slightly poorer inter-reader correlation [9, 18]. Smallest detectable differences have been estimated at less than 36% [9, 18, 19] for all measures, which has been compared favourably with clinical scores [9]. Recently, atlases have been produced to standardize scoring and facilitate inter-reader and inter-site comparisons [20, 21]. The reliability studies were performed before this, so performance may be improved by using the atlas; however, this remains to be demonstrated.

Several studies have applied the OMERACT scoring system to diagnosis, measurement of disease activity, prognosis and response to treatment (Tables 1 and 2). Low-grade changes have occasionally been seen in normal subjects [30]. Higher scores for oedema in the MCP joints have been found in RA compared with other types of inflammatory arthritis [23], suggesting a potential use in diagnosis. Synovitis and marrow oedema scores correlate with other measures of inflammation such as ESR, CRP and radiolabelled nanocolloid uptake while erosion score correlates with ESR [25]. OMERACT scores appear more sensitive to early erosions than plain X-rays [31], but not to long-term progression [29]. Importantly, synovitis, oedema and erosion scores all predict erosive progression [26, 27]. In patients receiving anti-TNF-α therapy there was a significant reduction in scores of synovitis (after 3 months) and marrow oedema (after 1 month) with significantly less erosive progression at 1 yr [28, 32].

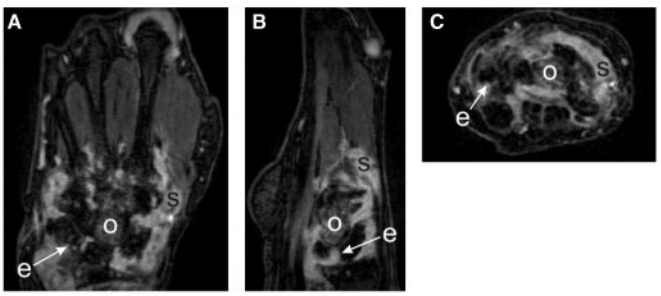

FIG. 1. T1-weighted post-contrast fat-suppressed images through the wrist and MCP joints of a patient with long-standing, active RA. (**A**) coronal, (**B**) sagittal and (**C**) axial sections showing examples of synovitis (s), erosion (e) and bone marrow oedema (o). Images acquired using 3D fat-suppressed VIBE sequence at 3 T (TR = 8 ms, TE = 4 ms, flip-angle = 30°, 0.5 mm isotropic resolution).

TABLE 1. Selected cross-sectional studies performed using the OMERACT RAMRIS system

Ref.	No. of patients	Results
[22]	4	Bone marrow oedema correlates with pain, CRP and histological osteitis.
[23]	16	MCP erosion significantly greater in RA patients than arthralgia patients.
[24]	28	No significant difference between RA and SLE/Sjögren scores.
[25]	28	Synovitis, oedema correlate with ^{99m}Tc nanocolloid uptake.

OMERACT scores are the most mature quantitation system for RA. They are straightforward, appear moderately reliable and sensitive, correlate with other measures of inflammatory activity, predict erosive progression and respond to treatment. They are robust, have been extensively validated and are suitable for multi-centre trials. They have the advantage of assessing synovitis, marrow oedema and erosions. Despite this, surprisingly few clinical trials to date have used OMERACT scoring, perhaps because of the relatively poor sensitivity to synovial change. Alternative methods for assessing synovitis are available (see subsequently) but there are no significantly better methods of assessing erosions and currently no alternative methods of assessing marrow oedema, an important marker for erosive progression.

Volume measurements

Synovial volume

In an effort to improve on the reproducibility and sensitivity of scoring systems, various techniques have been put forward for the direct measurement (in cubic millimetres or millilitres) of synovial volume.

As with OMERACT scoring, visualization of the inflamed synovium for volume measurement requires intravenous contrast to reliably exclude other tissues. Synovial volumes measured using unenhanced images are larger than those measured from enhanced images [33] due to variable additional contributions from underlying connective tissue, poorly vascularized, fibrous pannus and joint fluid. Enhancing synovitis is generally measured as it corresponds to active, inflamed tissue and is therefore expected to be a better marker of disease activity. Higher contrast doses improve synovial conspicuity and slightly increase the measured volume of enhancing tissue [34]. Strongly T1-weighted MR sequences optimize contrast between the enhancing synovitis and the surrounding tissues. While the precise protocol affects the delineation of the edges of the synovium, in particular the outer border, this is rarely important unless comparing images acquired with different imaging parameters. The delay between contrast administration and scanning is important as the volume of enhancing synovitis increases initially (see subsequently) before stabilizing after about 4 min. After 6–11 min contrast reaches the synovial fluid [35, 36], obscuring the synovium/fluid interface. Imaging is, therefore, best performed between these times. Post-contrast images are the most important but pre-contrast images [33, 35] or subtraction images [37] can be helpful to confirm enhancement. Subtraction images increase the conspicuity of enhancing synovitis, making differentiation from fatty marrow easier, although noise is increased and the anatomical relationships are less obvious. Movement

TABLE 2. Selected longitudinal studies performed using the OMERACT RAMRIS system

Ref.	No. of patients	Treatment	Time points	Results
[26]	27	DMARDs	0, 1, 2 y	Erosive progression correlates with clinical response Initial oedema and synovitis correlate with erosive progression
[27]	17	Anakinra	0, 3, 9 m	MR erosive progression at 3 m correlates with X-ray progression at 9 m Synovitis and erosions correlate with erosive progression No significant response to treatment
[28]	20	Infliximab	0, 4, 14, 54 wk	↓ Synovitis after 14 wk ↓ Oedema after 4 wk ↓ Erosions after 54 wk
[29]	47		0, 2 y	No clear benefit MRI over X-ray

wk, weeks; m, months; y, years.

during acquisition may introduce artefacts at the edges of subtracted images although these can be reduced by manual or automated registration prior to subtraction. In the absence of pre-contrast images, fat suppression may be useful [32]. Images oriented in the axial plane are often the most appropriate for analysis in the knee, wrist and hand [33, 37] although coronal sections are sometimes used in the wrist and hand [38]. Thin slices are advantageous, particularly at the edges of the synovium, and this can be achieved using 3D sequences [39, 40].

The most straightforward technique for measuring synovitis involves a skilled operator outlining the synovial tissue on each slice of an MR data set (Fig. 2). This has been reported in the knee, wrist and hand. Several studies have looked at the reproducibility of such measurements [37, 41, 42]. Intra-observer, inter-observer and inter-scan errors were around 5% in the knee [37] and slightly higher in the wrist [42] with combined reproducibility errors of 18% [37]. Changes of as little as 20% in synovial volume are detectable in the wrist [43], better than achievable using OMERACT scoring. Correlation between scoring and direct measurement ranged from moderate ($r = 0.7$) [43] to good ($r = 0.88$) [42]. In one study, synovitis volume measurement was a better predictor of erosive progression than OMERACT score [42].

Outlining the synovitis manually can take 1–2 hours per scan [33, 44, 45]. Thresholding in combination with rough manual outlining can substantially reduce analysis times, e.g. to 15 min [45]. Image intensity thresholds are set as percentage enhancements [45–47], relative to muscle [32, 48] or interactively [38, 49]. Other similarly enhancing tissues are excluded either by initial approximate outlining of the synovium [45, 48] or removal after thresholding [38, 49]. The choice of thresholding level is challenging and affects both reproducibility and accuracy. The reproducibility of such semi-automated measurements is poorer than manual outlining and is critically dependent on the threshold chosen, with an increase in overall reproducibility error of at least 6% compared with manual measurement [45]. This has been attributed to partial volume effects and synovial fluid enhancement, both of which could be minimized with a suitable imaging protocol. Volumes are significantly lower than those measured manually, but correlate well, particularly in the wrist. Automated identification using the technique of principle component analysis has also been successfully demonstrated [50]. An alternative approach to reducing imaging times by measuring the thickness of the synovium at 4 points, rather than the entire area of a slice [44], was less successful at reducing imaging times (45 min) and correlating with manual measures ($r = 0.7$). Semi-automated methods have been used to show correlations between synovial volume and clinical measures of disease activity [32, 38, 47, 49, 51] as well as responses to treatment [32, 49].

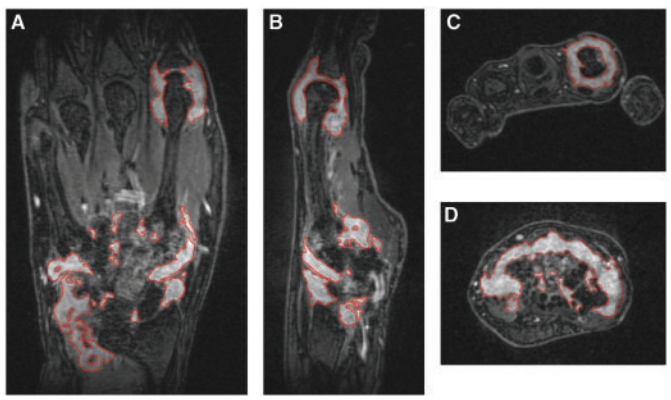

FIG. 2. Coronal (**A**), sagittal (**B**) and axial (**C**, **D**) sections through a 3D T1-weighted fat-suppressed image of the wrist and MCP joints. The volume of enhancing synovium has been manually outlined. Images acquired using 3D fat-suppressed VIBE sequence at 3T (TR = 8 ms, TE = 4 ms, flip-angle = 30°, 0.5 mm isotropic resolution).

Several studies have produced interesting results using measurements of synovial volume (Tables 3 and 4). Significant differences have been shown between RA patients and normal controls [55] or arthralgia patients [52], although not between rheumatoid and other inflammatory arthritides [52]. Correlations have been demonstrated with pain [32, 51], tenderness [49, 51], swelling [38, 47, 49, 51] and global clinical scores [32, 49] as well as with ESR [38] and metabolic activity on PET [51]. A dependence on anatomical location has been observed [40]. Comparison with histology in the knee has shown that the volume of synovitis is related to disease activity and correlates with overall histological inflammation, specifically fibrin deposition and cellular infiltration [54]. Correlation with vascular proliferation was weaker and was not significant with perivascular oedema. Evidence for synovial volume as a marker for disease progression comes from the correlation between synovial volume and erosive progression [39, 56, 60]. Synovial volume has also been shown to change in response to treatment. The decrease in synovial volume after synovectomy correlated with the duration of clinical remission [35]. Reduction in the volume of enhancing synovitis has been demonstrated with DMARDs [60] including methotrexate [51, 61], oral steroids [51] and anti-TNF-α therapy [32, 49]. A rapid response has been demonstrated to intra-articular steroids, with a significant decrease in synovial volume after 1 day [37], with longer remission in patients with smaller pre-treatment volumes.

Synovial volume correlates with histological markers of inflammation, rapidly demonstrates change with treatment and predicts erosive progression. It is, therefore, likely to represent a good marker for disease activity.

Bone erosion volume

Less work has been done looking at erosion volume compared with synovial volume, reflecting the difficulty in making accurate measurements of bone erosion.

Most studies have measured the volume of erosions by expert manual outlining. Post-contrast, T1-weighted images are useful for highlighting defects in the cortical bone necessary to diagnose an erosion [43]. They may, however, be insensitive to erosions filled with fibrous tissue [62]. Erosion volumes are usually measured in the coronal plane in the wrist [43, 58]. Although thin slices are expected to improve accuracy, this has not been clearly demonstrated [10].

Published work suggests reproducibility in the wrist is good, with intra-reader, inter-reader and inter-scan correlation

TABLE 3. Selected cross-sectional studies performed using direct volume measurement

Ref.	Tissue	Method	Joint	No. of patients	Results
[52]	S	Man	w, h	53	Synovitis greater in arthritis than arthralgia and similar in RA and other inflammatory arthritis
[53]	S, F	Man	k	13	Synovitis and fluid correlate with synovial YLK-40 and plasma PIIINP
[54]	S, F	Man	k	17	Synovitis correlates with histological markers of inflammation. Fluid correlates with swelling, tenderness
[42]	S	Man	w	26	Synovitis correlates with swelling, tenderness
[55]	S	Man	k	10	Synovitis more in active RA than inactive
[43]	E	Man	w	12	Erosion correlates with Joint Alignment Score

S, synovitis; F, synovial fluid; E, erosions; Man, manual outlining; w, wrist; k, knee; h, hand.

coefficients over 0.9 and good correlation with OMERACT scores [18, 43]. Both volume measurements and OMERACT scores are capable of detecting a similar (20%) difference in erosion volume [43]. Inter-observer agreement is poorer in the MCP joints [10, 18], with little evidence of benefit from training [18] or thinner slices [10]. This has been attributed to difficulty in estimating the proximal bone outline prior to erosion [18]. Erosion volume has been shown to correlate with the Joint Alignment and Motion score [10].

A semi-automated technique has allowed erosion volume to be calculated after manual outlining of the approximate joint area, using the combination of T1-weighted spin-echo and gradient echo images [58, 63]. Volumes correlated with erosion scores. A fully automated method has been demonstrated in a rat model of inflammatory arthritis [64]. The automated and semi-automated methods for determining erosion volume do not distinguish between oedema and erosions [58, 64]. Little work has been published looking at the independent quantitation of bone marrow oedema, despite evidence that this is important in predicting erosive progression [26, 65].

Thus, there is currently little evidence of any improvement in accuracy by using volume measurements of erosions compared with OMERACT scoring, particularly in the MCP joints. Automated and semi-automated scores may, however, provide time-saving advantages and do offer the potential to objectively measure bone volume loss in the future.

Synovial fluid volume

Synovial fluid volumes have been measured in the knee in RA. Strongly T2-weighted, unenhanced images allow the delineation of joint fluid from adjacent synovitis [47, 48]. Fluid segmentation has been performed manually [37, 46, 47] or using threshold values after initial rough manual outlining [48]. Reproducibility errors have been similar to those for synovitis with combined inter-reader, inter-scan errors of about 15% [37, 41] with good correlation with aspirated fluid volume [47].

Synovial fluid volume measured using MRI has been linked to potential synovial and plasma markers for RA [53]. A reduction in synovial fluid volumes has been shown after intra-articular steroids [37], arthroscopic [35] and radiation [47, 48] synovectomy.

Thus, synovial fluid volume may be reliably measured and has been shown to respond to intra-articular treatment in the knee. However, it is unclear that effusion volume offers any advantage over synovitis volume, and fluid volumes are unlikely to be as useful in the wrist and hand.

Cartilage volume

There is little published work quantitatively assessing cartilage in RA. Generalized cartilage thinning and focal cartilage erosion have been demonstrated in RA [66]. However, although numerous techniques for measuring cartilage volume and quality have been used in osteoarthritis, few have been applied to RA. A study on the knee of patients with RA measuring cartilage volume by manual segmentation of 3D gradient-echo images achieved inter-operator and inter-scan coefficients of variation of around 35% [59]. Cartilage volumes were lower than historical controls, however, no significant reduction in cartilage volume was detected over 1 yr. Cartilage measurement in the wrist and hand is difficult due to the small size of the joints [67]. Joint space narrowing was therefore excluded from the OMERACT system as reliability was poor [6]. Cartilage volume has been measured in cadaveric MCP joints to an accuracy of 2%, and the technique was successfully attempted in a single patient with RA [68]. T_2 measurement is widely used for assessing cartilage quality in osteoarthritis and has been shown to be reduced in juvenile RA [69].

While cartilage volume and T_2 measurements in the knee in particular hold promise for the future, they have not yet been used to demonstrate changes in RA as a result of disease progression or response to treatment.

Synovial volume measurements are relatively precise and reproducible, and compare favourably with OMERACT scoring. They offer increased sensitivity to change and less subjectivity, particularly when using semi-automated techniques. They are, therefore, preferable to OMERACT scoring where appropriate facilities are available. However, they are more dependent on the imaging technique and data about multi-centre use is lacking at present. There is currently little evidence for any benefit of erosion volume measurement over OMERACT scoring. The role of synovial fluid and cartilage volume measurement has yet to be established.

Dynamic contrast enhanced MRI

Dynamic contrast enhanced MRI (DCE-MRI) involves the acquisition of sequential images in rapid succession every few seconds during and after the intravenous administration of contrast agent.

TABLE 4. Selected longitudinal studies performed using direct volume measurement

Ref.	Tissue	Method	Joint	No. of patients	Time points	Treatment	Results
[32]	S	Semi	w	19	0, 14 wk	Infliximab	Synovitis correlates with pain, PGS, HAQ ↓ Synovitis after infliximab
[38]	S	Semi	w	13	0, 1 y	Adalimumab	Synovitis correlates with ESR, swelling ↓ Synovitis with adalimumab
[49]	S	Semi	w	16	0, 1 y	Infliximab	Synovitis correlates with swelling, tenderness, DAS28 ↓ Synovitis with infliximab
[48]	S, F	Semi	k	14	0, 4 m	Bq	↓ Fluid after Bq
[39]	S	Man	w, h	53	0, 1 y		Synovitis predicts erosive progression
[35]	S, F	Man	k	9	0, 1 d, 1 wk, 2 m, 1 y	Arth	↓ Synovitis and fluid at 2, 12 m. Synovitis at 2 m correlates with remission duration
[56]	S	Man	w	26	0, 3, 6, 12 m	Oral steroid	↓ Synovitis with DMARD at 6 m ↓ with DMARD + steroid at 3 m
[47]	S, F	Semi	k	16	0, 1 wk, 1 m, 3 m	Bq IA steroid	Synovitis and fluid correlate with soft tissue swelling ↓ Fluid after IA steroid
[37]	S, F	Man	k	15	0, 1 d, 1 wk, 1 m, 6 m	IA steroid	↓ Fluid and synovitis at 1 day after steroid ↓ Synovitis after 1 month only if clinical remission
[57]	S	Man	k	18	0, 1 m	Osmic acid	Relapse not correlated with synovitis
[51]	S	Semi	w	9	1, 2, 14 wk	Methotrexate	Synovitis correlates with FDG-activity. Change in synovitis correlates with change in FDG-activity, pain, tenderness, swelling
[58]	E, O	Auto	h	26	0, 3, 6, 24 m		↑ Erosions/oedema after 6 m
[59]	C	Man	k	23	0, 4, 12 m		No change in cartilage volume

Bq, radiation synovectomy; PGS, Patient Global Score; Arth, arthroscopic synovectomy; HAQ, Health Assessment Questionnaire; Auto, automated segmentation; Semi, semi-automated segmentation; Man, manual segmentation; O, oedema; C, cartilage; d, days; wk, weeks; m, months; y, years.

This allows the time-course of the synovial enhancement to be analysed. Measurements made from the enhancement curve (Fig. 3) are sensitive to various physiological parameters, including synovial perfusion and capillary permeability. Consequently, they are expected to be good markers for inflammation in RA.

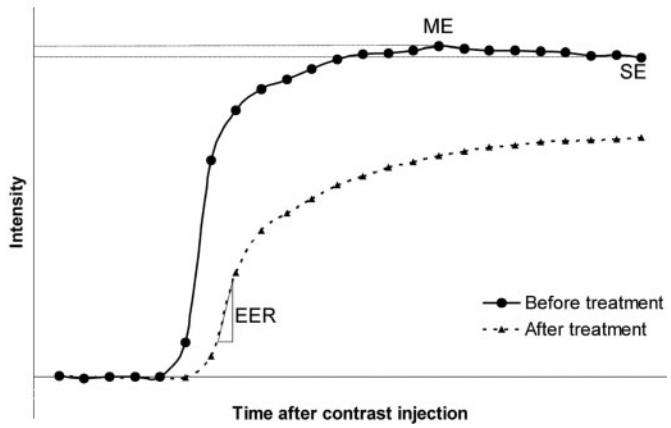

FIG. 3. Enhancement curves from a series of DCE-MRI images of a patient with RA showing the early enhancement rate (EER), the maximum enhancement (ME) and the late (static) enhancement (SE). Enhancement is reduced after anti-TNF-α therapy.

The knee and wrist/MCPs have been most commonly assessed in recent studies (Tables 5 and 6). DCE-MRI of the knee is technically easier due to the larger volumes of synovitis. Contrast is usually administered as a rapid, intravenous, bolus injection. This increases sensitivity to synovial vascularity but necessitates rapid imaging. A contrast dose of 0.1 mmol/kg gadolinium is usually given, but 0.05–0.3 mmol/kg have been used [3, 42]. Higher doses increase enhancement, but the effect is non-linear [34]. Injection rate directly affects the DCE-MRI measurements, hence consistency is important and a power injector may be helpful [87]. The conflicting demands of joint coverage, temporal resolution and spatial resolution are particularly important in DCE-MRI. Inflamed synovitis enhances rapidly over the first 20–30 s after a bolus of intravenous contrast (Fig. 3) and a temporal resolution of under 10 s is advantageous to accurately characterize the initial enhancement phase. The small size of the wrist and MCP joints means a spatial resolution of at least 1mm is helpful (Fig. 1). 3D sequences with high resolution in all three planes improve reproducibility in serial studies. Typically, images of the wrist from 3 mm slices acquired in under 30 s are adequate, although a wide range of imaging protocols have been used in different studies with temporal resolutions of 2.6–70 s [25, 75] and slice thicknesses from 1 to 7 mm [70, 88]. Imaging is usually carried out at 1.5T, although field strengths between 0.2 and 3T [25, 71, 88] have been used. In general, increased signal at higher field strengths allows better spatial and/or temporal resolution. In addition to high temporal and spatial resolution, the imaging

TABLE 5. Selected cross-sectional studies performed using DCE-MRI of RA

Ref.	Protocol	Voxel (mm)	Time	Plane	Slices	ROIs	Parameter	Joint	No.	Results
[70]	GE 30/12/70	$7 \times 0.8 \times 0.8$	20	sag	1	2	RE_{30}, RER_{55}	k	16	Correlates with PET, synovial thickness, static enhancement
[71]	SE 100/16	$5 \times 1.2 \times 0.9$	18	ax	3	Max	RER_{55}, MRE	w	36	Correlates with CRP, DAS, HAQ, ESR
[72]	SE 100/16	$5 \times 0.8 \times 0.9$	18	ax	3	Max	RER_{55}, MRE	w	30	No difference RA *vs* PsA
[73]	SE 180/20	$5 \times 1.2 \times 1.2$	48	sag	4	Max	MER	k	21	Correlates with histology, vascularity
[74]	GE 50/5/70	$5 \times 1 \times 1$	45	ax	1	1	MRER, MRE	s	43	Correlates with erosions
[75]	GE 8.5/4/10	$5 \times 1.3 \times 1.3$	2.6	cor	1	Slice	K^{PS}, K^{ep}, K^{el}	h	11	Greater in RA than OA/control
[76]	GE 30/12/70	$5 \times 1 \times 1$	8	sag	1	1	RER_{32}, MRE	k	12	Correlates with histological vascularity
[42]	GE 40/12/70	$5 \times 0.9 \times 0.6$	10	ax	1	Slice	RER_{55}	w	26	RER not proportional to synovial volume/ESR/CRP
[77]	GE 30/12/70	$7 \times 0.8 \times 0.8$	20	sag	1	Slice	$RER_{10\text{-}190}$	k	22	Correlates with clinical disease activity
[78]	GE 40/12/70	$5 \times 0.8 \times 0.8$	10	sag	1	Slice 4	RER_{55}, MRE	k	17	Correlates with overall histology, PMNL infiltration, fibrin, vessels, synovial multiplication, perivascular oedema, ESR, CRP
[25]	3D-GE 30/10/40	$2 \times 1.3 \times 0.6$	69	cor	12	3 max	ER_{69}	w	28	Correlates withTc-nanocolloid uptake, synovitis vol, marrow oedema, ESR
[79]	GE 11/5.3/60	5	6	sag	1	2	RER_{40}, MRE	k	13	Location dependent
[80]	GE 40/12/70	$3 \times 0.8 \times 0.6$	10	cor	1	Slice	RER_{55}	h	15	Higher in patients with PDUS signal
[81]	GE 40/12/70	$3 \times 0.8 \times 0.6$	10	cor	1	Slice	RER_{55}	h	15	Higher in patients with contrast enhanced PDUS signal

No., number of patients; SE, spin-echo; GE, gradient-echo; TSE, turbo-spin-echo; cor, coronal; sag, sagittal; ax, axial; RE_n, relative enhancement after n seconds; RER_n, relative enhancement rate over n seconds; ER_n, enhancement rate over n seconds; MRE, maximum/static relative enhancement; MER, maximum enhancement rate; MRER, maximum relative enhancement rate; s, shoulder; PDUS, power doppler ultrasound.

TABLE 6. Selected longitudinal studies performed using DCE-MRI of RA

Ref.	Protocol	Voxel (mm)	Time	Plane	Slices	ROIs	Parameter	No.	Joint	Time points	Results
[82]	GE 270/10/80	$3 \times 0.9 \times 0.8$	6	cor		4	RER_{max}	18	k/w	0, 1 m	Correlates with clinical findings ↓ With anti-TNFα treatment
[83]	FS-GE 150/9/60	$3 \times 0.5 \times 0.5$	42	cor	6	Max	ER_{42}, ME, RER_{42}	42	w	0, 1 y	Correlates with ESR, synovial volume, pain, shared epitope genotype, erosions at 1 yr ↓ With DMARD
[84]	GE 40/12/70	$5 \times 0.8 \times 0.8$	10	sag	1	Slice 4	RER_{55}	15	k	0, 1 d, 1 wk, 1 m, 6 m	↓ 1 wk after i.a. steroid Correlates with clinical relapse
[26]	3D-GE 30/10/40	$2 \times 1.3 \times 0.6$	69	cor	12	3 max	ER_{69}	27	w	0, 1, 2 y	Correlates with erosive progression
[85]	GE 30/5/60	5	8	sag		Vol	RER_{40}, MRE	34	k	0, 4 m	Greater response to leflunomide than methotrexate
[32]	GE 2.7/1/15	4	10	ax	11	1	$RER_{10–80\%}$ MRE	19	w	0, 14 wk	↓ After infliximab
[86]	GE 30/12/60	5	5	sag	1	2	MRER, MRE	12	k	0, 6 wk	Correlates with macroscopic appearance and CD4 histology

FS, fat suppressed; RER_{max}, relative enhancement rate to maximum enhancement; $RER_{10–80\%}$, relative enhancement rate between 10% and 80% of max enhancement; ME, maximum enhancement.

protocol must provide strongly T1-weighted images that are sensitive to the gadolinium. Most studies have therefore used rapid T_1-weighted gradient-echo sequences with relatively short echo times and repetition times. Although high flip angles are traditionally used for DCE-MRI [87], lower flip angles perform better at short repetition times [89].

The region of interest (ROI) of inflamed synovium from which the enhancement curve is determined may be chosen in different ways. This is important because there is evidence of variation in enhancement across the synovitis [25, 36, 79] corresponding to histological differences [78]. Combining multiple small ROIs improves results [25], analysing all the synovitis in a slice is better than using smaller ROIs [84] and multiple slices are better than a single slice [25]. Taken together these studies suggest the entire enhancing synovium should be included [90]. Because of the time involved in manually outlining all the inflamed synovium, several authors have used automated or semi-automated methods [40, 42, 50, 85].

Parameters that can be measured from the enhancement curve include the early enhancement rate, the maximum enhancement and the late or static enhancement (Fig. 3). The relative early enhancement rate (RER) is often used in preference to the absolute early enhancement rate as it is independent of the units of signal intensity and is proportional to the gadolinium concentration in the synovium (Tables 5 and 6). Theoretically the RER is more strongly dependent on synovial vascularity and capillary permeability than maximum enhancement or static enhancement and is therefore expected to be the best marker for disease activity in RA. Most studies measure the RER over a fixed time period between 30 and 60 s [42, 70, 72, 76, 78–81, 83–85]. Shorter periods increase the dependence on synovial vascularity but are technically more difficult. The relative enhancement at a fixed time [25, 26, 30, 91] is closely related to the RER. The early enhancement rate has been shown to correlate with erosions [74], ESR and pain [83], erosive progression [83] and effects of treatment [32, 85]. It has shown a better correlation with histology [78] and response to treatment [84] than the static enhancement. Direct measurements from the enhancement curve, such as the RER, have the disadvantage of depending on the precise imaging technique and equipment. They are also difficult to interpret as they have a complex dependence on the synovial pathophysiology. Recently, a different approach has been adopted by modelling the enhancement curves to determine underlying physiological parameters, including the volume transfer constant, K^{trans}. This depends predictably on synovial vascularity and capillary permeability, and is therefore expected to be a good marker for inflammatory activity [75, 88, 92–94].

Good intra-reader [25, 26, 72, 79, 83, 95], inter-reader [79, 84] and inter-scan [95] reproducibility (ICC > 0.9) has been demonstrated for DCE-MRI measurements. A median combined inter-scan/inter-reader difference of 26% was observed in the RER [84].

Evidence for the value of DCE-MRI comes from correlation with other measures of inflammation (in particular histology), prediction of disease progression and demonstration of a response to treatment.

DCE-MRI parameters have been shown to correlate with clinical findings including joint swelling [77], pain [76, 77] and disease activity score (DAS) [71], Paulus [82], ACR [91] and HAQ [71] scores. The picture with ESR is more confused with some studies finding a correlation [25, 78, 83, 96] while others were unable to do so [42, 82, 95], perhaps reflecting the dependence of the ESR on disease throughout the body. While enhancement parameters have shown differences between patients with RA and osteoarthritis [75], they have been unable to distinguish RA from psoriatic arthritis [72].

The enhancement rate correlates with other imaging measures of synovial volume, erosion, vascularity, capillary permeability and metabolic activity. Static MRI measures of enhancement [70] and synovial volume [70, 83] correlate with RER, implying a link between synovial vascularity and volume. Correlations have also been demonstrated with marrow oedema [25] and erosions [74], suggesting rapidly enhancing tissue is associated with erosive disease. Power Doppler vascularity, which directly images blood flow in the larger synovial vessels, also correlates with DCE-MRI [80, 81]. Correlations between enhancement rate and radiolabelled nanocolloid uptake are unsurprising since both depend on synovial vascularity and capillary permeability [25]. FDG-PET activity also correlates with the RER [70], suggesting a link between enhancement rate and metabolic activity.

Some of the most compelling evidence that DCE-MRI is likely to be a useful marker for disease activity comes from comparative studies with histology. The enhancement rate has been shown to correlate with overall histological inflammation [78, 95]. Strong correlations have been demonstrated between RER and vascularity (e.g. vascular area, proliferation) and perivascular oedema [73, 76, 78, 97]. This is more marked than those seen with synovial volume (see above), and supports the strong dependence of the RER on synovial vascularity and capillary permeability. Other histological markers of acute inflammation which have been linked with DCE-MRI include cellular and polymorphonucleocyte infiltration and fibrin deposition [78, 97]. No correlation has been observed with the more chronic changes of fibrosis [78], while links with granulation tissue are controversial [78, 97].

Two studies have compared baseline DCE-MRI with progression of bone erosion (defined by OMERACT scores) and have demonstrated a correlation between enhancement rate and erosive progression after 1 yr (42 patients) [83] and 2 yrs (24 patients) [26]. This provides evidence that DCE-MRI predicts erosive progression.

Several studies have demonstrated the effects of treatment on DCE-MRI measurements. The earliest changes have been shown after intra-articular steroid injection—a longitudinal study (15 patients) showed a decrease in enhancement rate in the knee 7 days after treatment [84]. Other studies have looked at the effects of DMARDs. A randomized controlled trial of 34 patients compared leflunomide with methotrexate and demonstrated a significant fall in RER after 4 months of leflunomide treatment, significantly greater than the response to methotrexate [85]. A small group of patients showed a fall in enhancement rate 14 months after starting methotrexate and hydroxychloroquine [91]. In a group of 42 patients, half of whom received DMARD therapy, a fall in enhancement rate was seen after 1 yr [83]. Three studies have looked at the effects of anti-TNF-α therapy. All showed a change in DCE-MRI after treatment. A statistically significant fall in enhancement rate of synovitis in the wrist was seen after 14 weeks of treatment in 19 patients [32]. A study of 18 patients showed a decrease in RER significantly greater than the control group after 4 weeks [82]. A further study of 12 patients using pharmacokinetic modelling demonstrated a decrease in K^{trans} with anti-TNF-α therapy but not with methotrexate [92]. DCE-MRI measurements have therefore been shown to respond to a variety of treatment regimens.

In summary, DCE-MRI should be performed using fast gradient-echo images with short echo times and repetition times allowing rapid imaging, ideally in 10 s or less. The relative early enhancement rate calculated from the entire volume of synovitis appears to be the best of the simple DCE-MRI measurements. It depends heavily on synovial vascularity and capillary permeability and as such is expected to be sensitive to inflammation. This is supported by correlation with clinical, laboratory, histological and other imaging measures of disease activity. Enhancement rates predict erosive progression and respond rapidly to treatment. They are therefore likely to be good measures of disease activity in RA.

The evidence to date suggests DCE-MRI is a more sensitive marker of disease activity than scored or measured synovial volume. It is therefore most likely to demonstrate changes in individual patients or cohorts. However, it is very dependent on

the precise experimental protocol, contrast injection and measurement technique so further work is needed before it can be applied to multi-centre studies.

Conclusion

MRI is well suited to providing quantitative measurements in RA because of its ability to visualize bone and soft tissues in three dimensions. The OMERACT scoring systems has been well validated and allows straightforward quantitation of bone erosions, bone marrow oedema and synovial volume, all of which predict erosive progression. Synovial volume can be measured directly by manually outlining the inflamed synovium, but this is time consuming. Semi-automated techniques have been developed that allow measurement in acceptable times. Such measurements may be more reproducible and sensitive than OMERACT scoring, correlate with histological inflammation and respond quickly to treatment. There is currently no clear advantage to direct measurement of erosion volume, but automated techniques under development may allow fast, objective measurements of bone loss. Finally, the use of dynamic contrast enhanced MRI provides measurements which reflect the underlying pathophysiology of the inflamed synovium and may provide the most responsive MR measurements of disease activity. DCE-MRI measurements have also been shown to correlate well with other measures of acute inflammation, predict erosive progression and to respond to treatment. However, the role of MRI measurements in routine clinical care for defining remission, determining optimal treatment and predicting long-term response to therapy remains to be established.

Rheumatology key messages

- Synovial volume, marrow oedema and erosions visualized on MRI predict erosive progression.
- Quantitation is by expert scoring or direct volume measurement.
- DCE-MRI measurements depend on inflammatory activity.

Acknowledgements

The authors wish to thank the Royal College of Radiologists, UK for a Research Fellowship.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Scott DL, Bacon PA. Joint damage in rheumatoid arthritis: radiological assessments and the effects of anti-rheumatic drugs. Rheumatol Int 1985;5:193–9.
2 Guillemin F, Billot L, Boini S, Gerard N, Odegaard S, Kvien TK. Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. J Rheumatol 2005;32:778–86.
3 Backhaus M, Burmester GR, Sandrock D *et al.* Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Ann Rheum Dis 2002;61:895–904.
4 Filippucci E, Iagnocco A, Meenagh G *et al.* Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. Clin Exper Rheumatol 2007;25:5–10.
5 Brenner W. 18F-FDG PET in rheumatoid arthritis: there still is a long way to go. J Nucl Med 2004;45:927–9.
6 McQueen F, Lassere M, Edmonds J *et al.* OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Summary of OMERACT 6 MR Imaging Module. J Rheumatol 2003;30:1387–92.
7 Lassere M, McQueen F, Ostergaard M *et al.* OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 3: an international multicenter reliability study using the RA-MRI Score. J Rheumatol 2003;30:1366–75.
8 Ostergaard M, Peterfy C, Conaghan P *et al.* OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003;30: 1385–6.
9 Conaghan P, Lassere M, Ostergaard M *et al.* OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 4: an international multicenter longitudinal study using the RA-MRI Score. J Rheumatol 2003;30:1376–9.
10 Bird P, Ejbjerg B, McQueen F, Ostergaard M, Lassere M, Edmonds J. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 5: an international multicenter reliability study using computerized MRI erosion volume measurements. J Rheumatol 2003;30:1380–4.
11 Schirmer C, Scheel AK, Althoff CE *et al.* Diagnostic quality and scoring of synovitis, tenosynovitis and erosions in low-field MRI of patients with rheumatoid arthritis: a comparison with conventional MRI. Ann Rheum Dis 2007;66:522–9.
12 Ejbjerg BJ, Narvestad E, Jacobsen S, Thomsen HS, Ostergaard M. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography. Ann Rheum Dis 2005;64:1280–7.
13 Eshed I, Althoff CE, Schink T *et al.* Low-field MRI for assessing synovitis in patients with rheumatoid arthritis. Impact of Gd-DTPA dose on synovitis scoring. Scand J Rheumatol 2006;35:277–82.
14 van der Heijde DM, van Leeuwen MA, van Riel PL *et al.* Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26–34.
15 Ostendorf B, Scherer A, Modder U, Schneider M. Diagnostic value of magnetic resonance imaging of the forefeet in early rheumatoid arthritis when findings on imaging of the metacarpophalangeal joints of the hands remain normal. Arthritis Rheum 2004;50:2094–102.
16 Haavardsholm EA, Ostergaard M, Ejbjerg BJ *et al.* Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting. Arthritis Rheum 2005;52:3860–7.
17 Ostergaard M, Klarlund M, Lassere M *et al.* Interreader agreement in the assessment of magnetic resonance images of rheumatoid arthritis wrist and finger joints–an international multicenter study. J Rheumatol 2001;28:1143–50.
18 Bird P, Joshua F, Lassere M, Shnier R, Edmonds J. Training and calibration improve inter-reader reliability of joint damage assessment using magnetic resonance image scoring and computerized erosion volume measurement. J Rheumatol 2005;32:1452–8.
19 Ejbjerg BJ, Vestergaard A, Jacobsen S, Thomsen HS, Ostergaard M. The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the Sharp/van der Heijde radiographic score. Arthritis Rheum 2005;52:2300–6.
20 Conaghan P, Bird P, Ejbjerg B *et al.* The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the metacarpophalangeal joints. Ann Rheum Dis 2005;64(Suppl 1):i11–21.
21 Ejbjerg B, McQueen F, Lassere M *et al.* The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. Ann Rheum Dis 2005;64(Suppl 1):i23–47.
22 McQueen FM, Gao A, Ostergaard M *et al.* High grade MRI bone oedema is common within the surgical field in rheumatoid arthritis patients undergoing joint replacement and is associated with osteitis in subchondral bone. Ann Rheum Dis 2007; DOI: 10.1136/ard.2007.070326 [epub ahead of print 9 May 2007].
23 Solau-Gervais E, Legrand JL, Cortet B, Duquesnoy B, Flipo RM. Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in the absence of anti-cyclic citrullinated peptide antibodies: a prospective study. J Rheumatol 2006;33:1760–5.
24 Boutry N, Hachulla E, Flipo RM, Cortet B, Cotten A. MR imaging findings in hands in early rheumatoid arthritis: comparison with those in systemic lupus erythematosus and primary Sjogren syndrome. Radiology 2005;236:593–600.
25 Palosaari K, Vuotila J, Takalo R *et al.* Contrast-enhanced dynamic and static MRI correlates with quantitative 99Tcm-labelled nanocolloid scintigraphy. Study of early rheumatoid arthritis patients. Rheumatology 2004;43:1364–73.
26 Palosaari K, Vuotila J, Takalo R *et al.* Bone oedema predicts erosive progression on wrist MRI in early RA–a 2-yr observational MRI and NC scintigraphy study. Rheumatology 2006;45:1542.
27 Ostergaard M, Duer A, Nielsen H *et al.* Magnetic resonance imaging for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis: a study of patients receiving combined anakinra and methotrexate treatment. Ann Rheum Dis 2005;64:1503–6.
28 Quinn MA, Conaghan PG, O'Connor PJ *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27–35.
29 Bird P, Kirkham B, Portek I *et al.* Documenting damage progression in a two-year longitudinal study of rheumatoid arthritis patients with established disease (the DAMAGE study cohort): is there an advantage in the use of magnetic resonance imaging as compared with plain radiography? Arthritis Rheum 2004;50:1383–9.
30 Ejbjerg B, Narvestad E, Rostrup E *et al.* Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. Arthritis Rheum 2004;50:1097–106.
31 Ejbjerg BJ, Vestergaard A, Jacobsen S, Thomsen H, Ostergaard M. Conventional radiography requires a MRI-estimated bone volume loss of 20% to 30% to allow certain detection of bone erosions in rheumatoid arthritis metacarpophalangeal joints. Arthritis Res Ther 2006;8:R59.
32 Tam LS, Griffith JF, Yu AB, Li TK, Li EK. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation. Clin Rheumatol 2007;26:941–6.

33 Savnik A, Malmskov H, Thomsen HS *et al.* MRI of the arthritic small joints: comparison of extremity MRI (0.2 T) vs high-field MRI (1.5 T). Eur Radiol 2001;11:1030–8.
34 Oliver C, Speake S, Watt I, Dieppe P, Ratcliffe G. Advantages of an increased dose of MRI contrast agent for enhancing inflammatory synovium. Clin Radiol 1996;51:487–93.
35 Ostergaard M, Ejbjerg B, Stoltenberg M *et al.* Quantitative magnetic resonance imaging as marker of synovial membrane regeneration and recurrence of synovitis after arthroscopic knee joint synovectomy: a one year follow up study. Ann Rheum Dis 2001;60:233–6.
36 Yamato M, Tamai K, Yamaguchi T, Ohno W. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. J Comput Assist Tomogr 1993;17:781–5.
37 Ostergaard M, Stoltenberg M, Gideon P, Sorensen K, Henriksen O, Lorenzen I. Changes in synovial membrane and joint effusion volumes after intraarticular methylprednisolone. Quantitative assessment of inflammatory and destructive changes in arthritis by MRI. J Rheumatol 1996;23:1151–61.
38 Zikou AK, Argyropoulou MI, Voulgari PV *et al.* Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab. J Rheumatol 2006;33:219–23.
39 Savnik A, Malmskov H, Thomsen HS *et al.* MRI of the wrist and finger joints in inflammatory joint diseases at 1-year interval: MRI features to predict bone erosions. Eur Radiol 2002;12:1203–10.
40 Tan AL, Tanner SF, Conaghan PG *et al.* Role of metacarpophalangeal joint anatomic factors in the distribution of synovitis and bone erosion in early rheumatoid arthritis. Arthritis Rheum 2003;48:1214–22.
41 Ostergaard M, Gideon P, Stoltenberg MB, Henriksen O, Lorenzen I. [Volumes of synovial membrane and joint effusion determined by MR imaging. Markers of severity and/or activity in rheumatoid arthritis?]. Ugeskr Laeger 1997;159:3956–61.
42 Ostergaard M, Hansen M, Stoltenberg M, Lorenzen I. Quantitative assessment of the synovial membrane in the rheumatoid wrist: an easily obtained MRI score reflects the synovial volume. Br J Rheumatol 1996;35:965–71.
43 Bird P, Lassere M, Shnier R, Edmonds J. Computerized measurement of magnetic resonance imaging erosion volumes in patients with rheumatoid arthritis: a comparison with existing magnetic resonance imaging scoring systems and standard clinical outcome measures. Arthritis Rheum 2003;48:614–24.
44 Savnik A, Bliddal H, Nyengaard JR, Thomsen HS. MRI of the arthritic finger joints: synovial membrane volume determination, a manual vs a stereologic method. Eur Radiol 2002;12:94–8.
45 Ostergaard M. Different approaches to synovial membrane volume determination by magnetic resonance imaging: manual versus automated segmentation. Br J Rheumatol 1997;36:1166–77.
46 Ostergaard M, Klarlund M. Importance of timing of post-contrast MRI in rheumatoid arthritis: what happens during the first 60 minutes after IV gadolinium-DTPA? Ann Rheum Dis 2001;60:1050–4.
47 Creamer P, Keen M, Zananiri F *et al.* Quantitative magnetic resonance imaging of the knee: a method of measuring response to intra-articular treatments. Ann Rheum Dis 1997;56:378–81.
48 Lee SH, Suh JS, Kim HS, Lee JD, Song J, Lee SK. MR evaluation of radiation synovectomy of the knee by means of intra-articular injection of holmium-166-chitosan complex in patients with rheumatoid arthritis: results at 4-month follow-up. Korean J Radiol 2003;4:170–8.
49 Argyropoulou MI, Glatzouni A, Voulgari PV *et al.* Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine 2005;72:557–61.
50 Klarlund M, Ostergaard M, Rostrup E, Skjodt H, Lorenzen I. Dynamic magnetic resonance imaging of the metacarpophalangeal joints in rheumatoid arthritis, early unclassified polyarthritis, and healthy controls. Scand J Rheumatol 2000;29:108–15.
51 Palmer WE, Rosenthal DI, Schoenberg OI *et al.* Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;196:647–55.
52 Savnik A, Malmskov H, Thomsen HS *et al.* Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases. J Rheumatol 2001;28:2193–200.
53 Volck B, Johansen JS, Stoltenberg M *et al.* Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. Osteoarthr Cartilage 2001;9:203–14.
54 Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, Volck B, Jensen CH, Lorenzen I. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium. Arthritis Rheum 1997;40:1856–67.
55 Ostergaard M, Gideon P, Henriksen O, Lorenzen I. Synovial volume–a marker of disease severity in rheumatoid arthritis? Quantification by MRI. Scand J Rheumatol 1994;23:197–202.
56 Ostergaard M, Hansen M, Stoltenberg M *et al.* Magnetic resonance imaging-determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. Arthritis Rheum 1999;42:918–29.
57 Ostergaard M, Stoltenberg M, Gideon P *et al.* Effect of intraarticular osmic acid on synovial membrane volume and inflammation, determined by magnetic resonance imaging. Scand J Rheumatol 1995;24:5–12.
58 Ostrowitzki S, Redei J, Lynch JA *et al.* Use of multispectral magnetic resonance imaging analysis to quantify erosive changes in the hands of patients with rheumatoid arthritis: short-term and long-term longitudinal studies. Arthritis Rheum 2004;50:716–24.
59 Gandy SJ, Brett AD, Dieppe PA *et al.* Measurement of cartilage volumes in rheumatoid arthritis using MRI. Br J Radiol 2005;78:39–45.
60 Ostergaard M, Hansen MS, Stoltenberg MB *et al.* [Magnetic resonance imaging as a marker of inflammation, destruction and prognosis in rheumatoid arthritis wrists]. Ugeskr Laeger 2000;162:4145–9.
61 Polisson RP, Schoenberg OI, Fischman A *et al.* Use of magnetic resonance imaging and positron emission tomography in the assessment of synovial volume and glucose metabolism in patients with rheumatoid arthritis. Arthritis Rheum 1995;38:819–25.
62 Perry D, Stewart N, Benton N *et al.* Detection of erosions in the rheumatoid hand; a comparative study of multidetector computerized tomography versus magnetic resonance scanning. J Rheumatol 2005;32:256–67.
63 Carano RA, Lynch JA, Redei J *et al.* Multispectral analysis of bone lesions in the hands of patients with rheumatoid arthritis. Magn Reson Imaging 2004;22:505–14.
64 Leung KK, Holden M, Saeed N *et al.* Automatic quantification of changes in bone in serial MR images of joints. IEEE Trans Med Imaging 2006;25:1617–26.
65 McQueen FM, Benton N, Perry D *et al.* Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1814–27.
66 Verstraete KL, Almqvist F, Verdonk P *et al.* Magnetic resonance imaging of cartilage and cartilage repair. Clin Radiol 2004;59:674–89.
67 Ostergaard M, Szkudlarek M. Magnetic resonance imaging of soft tissue changes in rheumatoid arthritis wrist joints. Semin Musculoskelet Radiol 2001;5:257–74.
68 Peterfy CG, van Dijke CF, Lu Y *et al.* Quantification of the volume of articular cartilage in the metacarpophalangeal joints of the hand: accuracy and precision of three-dimensional MR imaging. AJR Am J Roentgenol 1995;165:371–5.
69 Kight AC, Dardzinski BJ, Laor T, Graham TB. Magnetic resonance imaging evaluation of the effects of juvenile rheumatoid arthritis on distal femoral weight-bearing cartilage. Arthritis Rheum 2004;50:901–5.
70 Beckers C, Jeukens X, Ribbens C *et al.* (18)F-FDG PET imaging of rheumatoid knee synovitis correlates with dynamic magnetic resonance and sonographic assessments as well as with the serum level of metalloproteinase-3. Eur J Nucl Med Mol Imaging 2006;33:275–80.
71 Cimmino MA, Innocenti S, Livrone F, Magnaguagno F, Silvestri E, Garlaschi G. Dynamic gadolinium-enhanced magnetic resonance imaging of the wrist in patients with rheumatoid arthritis can discriminate active from inactive disease. Arthritis Rheum 2003;48:1207–13.
72 Cimmino MA, Parodi M, Innocenti S *et al.* Dynamic magnetic resonance of the wrist in psoriatic arthritis reveals imaging patterns similar to those of rheumatoid arthritis. Arthritis Res Ther 2005;7:R725–31.
73 Gaffney K, Cookson J, Blades S, Coumbe A, Blake D. Quantitative assessment of the rheumatoid synovial microvascular bed by gadolinium-DTPA enhanced magnetic resonance imaging. Ann Rheum Dis 1998;57:152–7.
74 Hermann KG, Backhaus M, Schneider U *et al.* Rheumatoid arthritis of the shoulder joint: comparison of conventional radiography, ultrasound, and dynamic contrast-enhanced magnetic resonance imaging. Arthritis Rheum 2003;48:3338–49.
75 Kirkhus E, Bjornerud A, Thoen J, Johnston V, Dale K, Smith HJ. Contrast-enhanced dynamic magnetic resonance imaging of finger joints in osteoarthritis and rheumatoid arthritis: an analysis based on pharmacokinetic modeling. Acta Radiol 2006;47:845–51.
76 Konig H, Sieper J, Wolf KJ. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. Radiology 1990;176:473–7.
77 Ostergaard M, Lorenzen I, Henriksen O. Dynamic gadolinium-enhanced MR imaging in active and inactive immunoinflammatory gonarthritis. Acta Radiol 1994;35:275–81.
78 Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, Volck B, Sonne-Holm S, Lorenzen I. Quantification of synovitis by MRI: correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. Magn Reson Imaging 1998;16:743–54.
79 Rhodes LA, Tan AL, Tanner SF *et al.* Regional variation and differential response to therapy for knee synovitis adjacent to the cartilage-pannus junction and suprapatellar pouch in inflammatory arthritis: implications for pathogenesis and treatment. Arthritis Rheum 2004;50:2428–32.
80 Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis Rheum 2001;44:2018–23.
81 Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Contrast-enhanced power Doppler ultrasonography of the metacarpophalangeal joints in rheumatoid arthritis. Eur Radiol 2003;13:163–8.
82 Kalden-Nemeth D, Grebmeier J, Antoni C, Manger B, Wolf F, Kalden JR. NMR monitoring of rheumatoid arthritis patients receiving anti-TNF-alpha monoclonal antibody therapy. Rheumatol Int 1997;16:249–55.
83 Huang J, Stewart N, Crabbe J *et al.* A 1-year follow-up study of dynamic magnetic resonance imaging in early rheumatoid arthritis reveals synovitis to be increased in shared epitope-positive patients and predictive of erosions at 1 year. Rheumatology 2000;39:407–16.
84 Ostergaard M, Stoltenberg M, Henriksen O, Lorenzen I. Quantitative assessment of synovial inflammation by dynamic gadolinium-enhanced magnetic resonance imaging. A study of the effect of intra-articular methylprednisolone on the rate of early synovial enhancement. Br J Rheumatol 1996;35:50–9.
85 Reece RJ, Kraan MC, Radjenovic A *et al.* Comparative assessment of leflunomide and methotrexate for the treatment of rheumatoid arthritis, by dynamic enhanced magnetic resonance imaging. Arthritis Rheum 2002;46:366–72.

86 Veale DJ, Reece RJ, Parsons W *et al.* Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology. Ann Rheum Dis 1999;58:342–9.
87 Buckley DL, Parker GJM. Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. In: Jackson A, Buckley DL, Parker GJM, eds. Dynamic contrast enhanced magnetic resonance imaging in oncology. Berlin: Springer, 2003;69–79.
88 Hodgson RJ, Connolly S, Barnes T, Eyes B, Campbell RSD, Moots R. Pharmacokinetic modeling of dynamic contrast-enhanced MRI of the hand and wrist in rheumatoid arthritis and the response to anti-tumor necrosis factor-α therapy. Magn Reson Med 2007;58:482–9.
89 Dale BM, Jesberger JA, Lewin JS, Hillenbrand CM, Duerk JL. Determining and optimizing the precision of quantitative measurements of perfusion from dynamic contrast enhanced MRI. J Magn Reson Imaging 2003;18:575–84.
90 McQueen FM, Crabbe J, Stewart N. Dynamic gadolinium-enhanced magnetic resonance imaging of the wrist in patients with rheumatoid arthritis: comment on the article by Cimmino et al. Arthritis Rheum 2004;50:674–5, author reply 675–6.
91 Lee J, Lee SK, Suh JS, Yoon M, Song JH, Lee CH. Magnetic resonance imaging of the wrist in defining remission of rheumatoid arthritis. J Rheumatol 1997;24:1303–8.
92 Gardener JC, Aierhut ML, Gardner GC *et al.* Vascularity in the RA wrist at 1-2 months following Initiation of anti-TNFalpha and methotrexate therapy. Rheumatology 2003;47:S131.
93 Workie DW, Dardzinski BJ, Graham TB, Laor T, Bommer WA, O'Brien KJ. Quantification of dynamic contrast-enhanced MR imaging of the knee in children with juvenile rheumatoid arthritis based on pharmacokinetic modeling. Magn Reson Imaging 2004;22:1201–10.
94 Workie DW, Dardzinski BJ. Quantifying dynamic contrast-enhanced MRI of the knee in children with juvenile rheumatoid arthritis using an arterial input function (AIF) extracted from popliteal artery enhancement, and the effect of the choice of the AIF on the kinetic parameters. Magn Reson Med 2005;54:560–8.
95 Gaffney K, Cookson J, Blake D, Coumbe A, Blades S. Quantification of rheumatoid synovitis by magnetic resonance imaging. Arthritis Rheum 1995;38:1610–7.
96 Nagele M, Kunze V, Koch W *et al.* [Rheumatoid arthritis of the wrist. Dynamic Gd-DTPA enhanced MRT]. Rofo 1993;158:141–6.
97 Tamai K, Yamato M, Yamaguchi T, Ohno W. Dynamic magnetic resonance imaging for the evaluation of synovitis in patients with rheumatoid arthritis. Arthritis Rheum 1994;37:1151–7.