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**The relationship between synovial pathobiology and MRI abnormalities in  
RA : a systematic review**

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Key words: Magnetic resonance imaging, synovitis, pathobiology, rheumatoid  
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**running foot note: MRI, synovitis, pathobiology**

## **Abstract**

### **Objectives**

Magnetic Resonance Imaging (MRI) has been increasingly recognized as a critical tool for the assessment of patients with rheumatoid arthritis (RA) and is able to reliably identify synovitis, bone marrow oedema, bone erosion and joint space narrowing/cartilage loss. Understanding the exact relationship between each MRI feature and local synovial pathobiology is critical in order to dissect disease pathogenesis as well as develop future predictive models.

### **Methods**

Therefore a systematic review of the current published literature examining the relationship between MRI abnormalities and synovial pathobiology in patients with RA was performed.

### **Results**

Eighteen studies were identified; most focused on validation of MRI as a tool to detect and quantify synovitis with a significant relationship demonstrated. Additionally from the limited data available a critical role for synovial pathways at least in driving joint damage seems likely. However there was a lack of data examining the relationship between synovial pathobiology and bone marrow abnormalities and joint space narrowing.

### **Conclusions**

Although understanding the inter-relationship of these disease biomarkers offers the potential to enhance the predictive validity of modern imaging with concomitant synovial pathobiological analysis, further studies integrating MRI

with synovial tissue analysis, in well controlled cohorts at distinct disease stages, before and after therapeutic intervention are required in order to achieve this.

## **Introduction**

Magnetic resonance imaging (MRI) is an excellent tool to delineate pathology in rheumatoid arthritis (RA) as it is able to define bone, cartilage, fluid and soft tissues. This is possible as MRI is able to delineate structures with high water content on T2 -weighted (T2w) fat suppressed or short tau inversion recovery (STIR) sequences and following injection of gadolinium-DTPA, (Gd-DTPA) regions of high vascularity. Thus feasibly MRI can quantify both synovial volume and inflammation and act as a surrogate non-invasive marker of histological inflammation. Specific MRI features of RA synovial joints have been demonstrated to be of particular prognostic value: synovitis, bone marrow oedema (BME), bone erosions and cartilage thinning. MRI has the capacity to detect bone erosions two years earlier(1) than plain radiographs and sensitivity to detect change even in small cohorts(2), an effect that is of critical relevance given the capacity of improved treatment algorithms to halt joint damage(3). Consequently MRI is now well recognized as a robust outcome measure in clinical trials.

Historically the pathological events leading to joint damage in RA have been suggested to be a sequence of primary synovitis leading to BME, cartilage thinning and finally erosions. There is increasing data to challenge this paradigm. Firstly although a significant relationship between BME and synovitis (4) and between synovitis and the development of bone erosions has been demonstrated(5) debate regarding the exact contribution of synovitis/BME in

initiating and/or sustaining bone erosion continues (6) with some evidence suggesting that BME *per se* maybe an independent predictor of erosive progression (4,7–13). Furthermore there is evidence primarily from MRI studies to support a biomechanical effect on erosive progression(14). Secondly MRI studies have noted BME and erosions as early events with cartilage thinning occurring later(15). Thirdly a number of radiographic studies have reported an incongruent relationship between cartilage thinning and erosions(15,16). Finally recent data have demonstrated an association between MRI documented BME, synovitis, baseline cartilage damage and subsequent cartilage loss(17). These observations raise a number of fundamental questions regarding mechanisms of joint damage and in particular whether synovial pathobiological pathways initiate and/or sustain a local environment that drives BME, erosions and/or cartilage thinning.

It was within this context that a systematic literature review was conducted to assess published data investigating the relationship between RA synovial pathobiology and MRI BME, synovitis, erosions and cartilage thinning.

## **Methods**

The study methodology was conducted in line with PRISMA guidelines(18) and was registered with PROSPERO ([http://www.crd.york.ac.uk/NIHR\\_PROSPERO](http://www.crd.york.ac.uk/NIHR_PROSPERO), registration CRD42016033875). As this was a systematic review no ethics approval was sought in accordance with the policy of Barts Health NHS Trust.

## **Search Strategy**

Relevant articles, reviews and abstracts were identified through an initial search of EMBASE, MEDLINE and the Cochrane Library for articles published up to March 2016. The MEDLINE MeSH keyword search terms (Rheumatoid arthritis, rheumatoid and arthritis, RA, rheumatoid, inflammatory arthritis, nuclear magnetic resonance imaging, magnetic AND resonance AND imaging, synovitis, synovi, pathology, histopathology, immunohistochemistry, pathol, histo, immune, joint surgery, arthroscopy, biopsy, joints, surgery) and Boolean operators adopted are presented in Table 1. These were modified to accommodate each search database. EMBASE and Cochrane search terms are presented as supplementary data (Supplementary Tables 1 and 2 respectively).

### **Eligibility criteria**

Studies including RA patients undergoing a MRI scan of a peripheral synovial joint along with sampling of synovial tissue were eligible. Outcome measures for MRI scanning included BME, joint erosion, synovitis and cartilage thickness. Outcome measures for synovial tissue included macro/microscopic histological assessment and immunohistochemical and gene expression analysis. In order to be included within the review studies had to directly compare one MRI RA feature with one or more synovial outcome measure. All types of study design were included and analysis was restricted to humans. Non English language articles with no translation available and abstracts with no corresponding full text article were excluded.

Two reviewers (F.H. and A.M.) independently reviewed the titles and abstracts from potentially relevant articles identified through the search strategy. Both reviewers assessed the full texts of all potentially eligible articles.

### ***Data extraction***

Data were entered onto a pre-defined data extraction table. For each study the following data were recorded regarding study design: type of study, disease stage (e.g. early vs. established disease), procedure for synovial sampling, time interval between synovial sampling and MRI scan, whether concomitant DMARD and/or steroid therapy was controlled for, joint imaged and joint biopsied. The following MRI parameters were also recorded: MRI feature scored, acquisition strength and method of assessment of MRI features. Additionally the following parameters regarding synovial tissue analysis were recorded: number of synovial samples taken, procedure for synovial tissue preparation, macroscopic assessment of synovium, histological assessment of H&E stained samples, immunohistochemical assessment, synovial gene expression analysis and main conclusions. Data extraction was performed by one reviewer (F.H.) and was verified by a second (A.M). Any disagreements regarding data extraction were resolved following discussion between the reviewers.

### **Quality assessment**

The quality of each study was independently assessed by two reviewers (FH and AM) using an adapted standardized quality scoring tool (Supplementary data Table 3) (19,20) to assess the following components: i. study population, ii. MRI assessment and scoring, iii. Histological assessment, and iv. Study design and analysis and data presentation. A score of '1' or '0' was allocated for each question according to whether the study fulfilled the criteria or not respectively.

A study was considered to be high quality if it exceeded or equaled the mean score (% of total) in its class (cross sectional vs RCT vs cohort study).

## **Results**

### **Search Strategy**

A summary of the results of the search strategy is presented in the PRISMA flow chart shown in Figure 1. This indicates that a total of 444 articles were identified. Following the exclusion of duplicates (n=117) and review articles (n=103) 224 articles were screened. Of these 188 were excluded (122 as didn't include patients with RA, 54 as didn't include histopathological analysis of synovial tissue, 7 as examination of tissue in vitro or in animal models and 5 as no MRI scans were included). Of the remaining 36 articles 18 were then excluded: 2 as no English translation available, 5 as no synovial histopathobiological examination (3 no synovial histology and 2 as synovial explants in vitro only), 1 as no comparison of MRI and synovial pathobiology (not relevant to task), 4 as did not include patients with RA and 6 as abstract only with no full text. 18 articles were then identified that satisfied the eligibility criteria and were therefore included in the review.

### **Characteristics of included studies**

A summary of the characteristics of the 18 studies is presented in Table 2 (MRI characteristics) and Table 3 (histopathobiological characteristics). A total of 442 participants were included in the analyses from the 18 studies. 327 of these had RA, 19 spondyloarthropathy, 4 psoriatic arthritis, 55 osteoarthritis, 2 healthy



controls and 35 other arthritic conditions. 11 studies were cross sectional observational studies (21–31) and one study was a retrospective analysis(32). Four studies were prospective open label clinical trials(33–36), one study was a blinded randomized clinical trial (RCT)(37) and one study was a prospective observational clinical study(38). Fifteen studies included patients only with established RA (although exact disease duration was not specified in two of these studies(31,35)and three studies specifically included patients with disease duration of <2 years (26,36,38). 14 studies sampled synovium from the knee joint and 4 studies included samples from small joints(26,31,32,35). Variable methods for synovial sample retrieval were reported: 7 studies utilizing arthroscopy (29,31,33,34,36–38), 4 arthroplasty (21,27,28,32) and three using both (22,23,30). Two studies used blind needle biopsy (24,25) and two mini-arthroscopy (Table 2)(26,35). Acquisition of images was performed on a 1.5T MRI scanner with contrast administration in 13 studies(21–23,26–30,32–34,36,37) and without in one study(38). Two studies used a 0.5T + contrast administration (Table 2) (24,25) and two a 3T+ contrast protocol (31,35) although the latter study used a 0.2T scanner in a significant proportion of patients (4/10) with claustrophobia.

### **Quality Assessment of Studies**

A summary of quality scoring of studies is provided in supplementary data (Supplementary Table 4). Quality scores were converted to percentages of the maximum score within each class of study. The mean (range) quality score was 56% (25–75) for cross sectional studies and 68% (46–93) for cohort studies indicating a broad range of scores. The one RCT had a quality score of 71%.

## **Clinical results**

### **Synovitis**

MRI synovitis can be assessed by static and dynamic protocols. Subsequent to the acquisition of T1 weighted images (Figure 2A) static protocols assess the volume of enhancing synovitis following the administration of a gadolinium-based contrast agent (Figure 2B) at a fixed time point. Synovitis volume can then be assessed manually or using a semi automated method by outlining the synovial tissue. Static images can also be assessed using the widely validated semi-quantitative OMERACT-RAMRIS synovitis score(39). Dynamic contrast enhanced (DCE)-MRI involves the rapid acquisition of sequential images during and after administration of contrast and assesses rate of enhancement of synovial tissue. Results can be influenced by factors such as synovial perfusion and capillary permeability: thus dynamic versus static protocols maybe able to more sensitively reflect local synovial inflammatory activity (40,41).

### ***Does MRI synovitis reflect histopathological inflammation?***

16 studies were identified that directly examined the relationship between the degree of MRI synovitis and local synovial pathobiology(21–25,27–33,35–37). Macroscopic synovitis and MRI synovitis was assessed in three studies both semi-quantitatively(22) and using dynamic MRI protocols (34,37) with all three suggesting a significant correlation between macroscopic and MRI synovitis. Six studies (21–24,28,31) using dynamic MRI and three studies (26,27,32) using static MRI protocols also directly examined the relationship between MRI determined synovitis and synovial inflammation assessed microscopically

following routine H&E staining. 8/9 of these studies (21–24,26–28,31) concluded that histological inflammation correlated with either semi-quantitative or DCE MRI synovitis. Although immunohistochemical analysis of the synovial cell infiltrate was performed in seven studies(27,29,31,33,35–37) only six directly reported the relationship between histological markers and synovitis with a significant relationship between MRI synovitis and: CD4+ T cells (37), CD68+ sublining macrophage number(27,29,31)cell proliferation (Ki67) (27) and neoangiogenesis (CD31)(27) reported. 3/4 studies also reported a significant relationship between MRI synovitis and degree of histological vascularity through: semi-quantitative assessment of H and E stained tissues (30) expression of the neoangiogenesis marker CD31(27), endothelial cell marker QBend30 (25) and vWF expression (36). Conversely Vordenbaumen et al (35) reported no significant relationship between either sublining macrophage number or vascular endothelial growth factor (VEGF) (an immunohistochemical marker of vascularization) and RAMRIS synovitis.

***Does MRI synovitis capture modulation of synovial pathobiology following effective therapeutic intervention?***

Longitudinal data examining whether MRI is sensitive enough to detect modulation of histological synovitis following effective therapeutic intervention was evaluated in four studies incorporating serial MRI scans and paired synovial biopsies. Firstly an open label placebo controlled study of intra articular anti-CD4(37) reported a significant correlation between MRI synovitis and macroscopic synovitis with a trend towards improvements in both histological and MRI synovitis only in patients receiving active treatment. Secondly Buch et al

(33) in a prospective open label trial reported on the synovial effect of abatacept in a cohort of 13 patients. Although this study did not report directly on the relationship between modulation of MRI synovitis and synovial histology it did report on the relationship between synovial gene expression and MRI synovitis, documenting a significant association between down regulation of the T cell cytokine IFN $\gamma$  and reduction in MRI synovitis scores in responders to treatment. Thirdly a prospective open label trial of 16 RA patients investigated the effect of TNF inhibitor therapy on hypoxia, macroscopic and microscopic synovial inflammation and MRI synovitis(34). Patients underwent a baseline needle arthroscopic synovial biopsy and DCE MRI of the knee both of which were repeated 3 months after starting anti-TNF therapy. This study demonstrated a significant inverse relationship between hypoxia and clinical response to anti-TNF therapy. The investigators also looked directly and found a significant relationship between macroscopic synovitis/vascularity and MRI synovitis. There were also significant associations demonstrated between falls in CD4+ T cells and CD68+ sublining macrophages and MRI synovitis. Finally Vordenbaumen et al(35) reported results from six patients who underwent sequential MCP joint biopsy and MRI and reported no significant association between change in sublining macrophage number and RAMRIS synovitis score although given the small sample size the significance of the results is unclear.

The data identified within this review provides an initial basis for the use of MRI as a surrogate measure of histological synovitis. Of particular importance is the relatively consistent demonstration of a significant relationship between CD68+ sublining macrophage number and MRI synovitis, the only current synovial biomarker validated as a measure of disease activity(42). However it is also

important to consider a number of limitations when interpreting results from these studies(21–23,25–30,35,37). Firstly it is now recommended that in order to overcome significant synovial pathological heterogeneity 6 synovial samples from different sites should be analysed for large joint procedures (43) and 4 for small joints (44). Although ten studies reported number of synovial samples retrieved per procedure (21–23,26,28,30,33,35,37,38) only four cohorts reported retrieving 6 or more biopsies(30,31,33,35). Furthermore only a selected number of studies specified a biopsy site predetermined by the MRI image (21–23,28,30,37) and so were able to directly compare local synovial pathology. Synovial pathology is also influenced by disease course as well as therapeutic intervention(45–47) factors that were not routinely controlled for in a number of studies (21–23,28,30,32) as a wide variability in time from MRI assessment to synovial sampling was reported. In addition, only two studies(21,29) reported that intra articular steroid injections were not permitted in this period and only three studies(29,33,37) controlled doses of steroids and DMARDs prior to study inclusion. It should also be noted that the majority of studies identified harvested synovial tissue from arthroplastic knee joint procedures (21–23,27,28,30,32), which restricts sampling of tissue to end stage joints. Indeed there was only limited data evaluating pathobiology at distinct disease stages from homogenous cohorts with only one study(29) including patients specifically with disease duration of less than 1 year and only two studies(26,38) including patients with disease duration of less than two years (26,38). Importantly of the 18 studies identified thirteen sampled knee joints, with only four (26,31,32,35) examining the relationship in small joints.

### **Bone marrow oedema**

MRI is unique amongst currently available imaging modalities in its ability to detect BME (Figure 2C) and although outside the remit of this systematic review it is worth noting that BME has been shown to equate to histological osteitis(48). Importantly the occurrence of BME has been tightly correlated with the presence of synovitis (49), however whether BME is driven and/or maintained by synovial pathobiological signals is unknown and very limited data examining this relationship was identified. Takase et al(27) report that in a cohort of 15 RA patients no significant relationship between histopathological changes of inflammation (neovascularization, inflammatory cell infiltrates and lining layer thickness) and MRI BME were found. In a further cohort of 7 patients in clinical remission(32), no correlation between MRI BME and histological synovitis was reported; this is likely to be explained by the small number of patients within the study. Finally in a cohort of ten patients Vordenbaumen et al (35) report that synovial staining for VEGF significantly correlated with RAMRIS BME scores in MCP joints. Certainly more complex synovial analysis in larger cohorts at different stages of disease will be required to fully interpret whether synovial signals are involved or required in the initiation and/or maintenance of BME.

### **Bone erosion**

MRI has been increasingly recognized as a more sensitive marker of erosions (Figure 2D) than plain radiography(50). The validation of the OMERACT-RAMRIS MRI score(39) as a robust and sensitive tool to document presence and/or erosive progression in patients with RA suggests that incorporating MRI progression data with synovial pathobiology may reveal important signatures of

disease. In two cross sectional cohorts Andarajah et al (32) reported in 7 patients with established RA no clear association between histological synovitis and erosions(32) and Vordenbaum (35) et al reported a significant relationship between synovial VEGF staining and the RAMRIS erosive score in MCP joints in 10 patients. Interpretation of the significance of these results is complicated by the small numbers, cross sectional approach and lack of validated MRI erosion score in the former report. However in a prospective study of 60 patients Kirkham et al (38) who aimed to examine whether synovial pathobiology could explain joint damage progression, as assessed by progression in the OMERACT-RAMRIS score(51). Although the authors identified no specific synovial histological features, using multivariate analysis of gene expression they identified IL-1, TNF $\alpha$ , IL-17, and IL-10 as predictive of joint damage progression. This study had a number of limitations, namely i) a wide range of disease duration in patients recruited to the study, ii) lack of control of concomitant disease modifying therapies and iii) joint damage progression in the small joints of the hands was related to distant synovial sampling sites in the knee. Notwithstanding this the report is highly instructive in identifying synovial mediators of joint damage progression and it remains important therefore to validate the results in further larger cohorts of therapy naïve early RA patients.

### **Cartilage loss**

Cartilage loss in RA can be assessed by documenting joint space narrowing on plain radiographs as well as MRI (Figure 2E). However no data was identified within this systematic review to examine the relationship between cartilage loss and synovial pathobiology. .

## **Discussion**

MRI has significant advantages over other imaging techniques for patients with RA; it does not expose patients to ionising radiation, it can sensitively detect synovitis, erosions and joint space narrowing and is unique in its capacity to detect BME. This differentiates MRI from ultrasound which although is a sensitive measure of histological synovitis (52) can not detect BME and does not have validated outcome measures for cartilage loss or bone erosion. The clinical studies identified in this review indicate a significant relationship between histological and MRI evident synovitis, which is important to validate MRI as a tool to reliably assess synovitis without the need for invasive biopsy. Furthermore from the limited data available a critical role for synovial pathways at least in driving joint damage(38) seems likely but requires more extensive validation. However overall the data provides limited information on the specific synovial pathobiological processes driving MRI abnormalities in RA.

Although the past decade has seen tremendous advances in the care of patients with RA considerable challenges remain. These include: i) specificity/sensitivity of current diagnostic/classification criteria for RA, ii) prediction of prognosis following diagnosis of RA, and iii) limited biomarkers of response/resistance to biologic drugs. What is required is a move towards an era of personalised medicine for patients with RA, with targeted treatment pathways from diagnosis, but this is only possible if critical pathways mediating both disease pathogenesis and clinical response to therapy are further elucidated. What this review highlights is the need to validate the relationship between synovial pathobiology and MRI abnormalities at the single joint level both in well defined early and



established RA cohorts and within clinical trial protocols of established and novel biologic drugs. This is particularly important as historical limitations such as the lack of sensitivity of clinical examination and radiographic assessment to detect synovitis and joint damage progression/cartilage loss respectively are largely overcome by the advent of a robust validated MRI score capable of assessing synovitis and erosion(39) and potentially BME and cartilage loss (53). Furthermore the advent of techniques such as ultrasound guided synovial biopsy (Figure 3) that provide a technically simple, minimally invasive approach to tissue acquisition from small as well as large joints(54), and more recent techniques to rapidly and simultaneously examine the expression of multiple genes are likely to overcome challenges in sampling tissue from previously inaccessible joints and variability in histological assessment of synovial tissue.

Overall the data identified within this systematic review validates MRI as a tool to assess synovitis but very limited data directly examining the link between synovial pathobiology and joint damage/cartilage loss and BME was identified. . Future research should focus on clinical trial protocols integrating synovial sampling with MRI imaging at different stages of disease in order to dissect critical synovial pathways mediating RA pathogenesis. Although understanding the inter-relationship of these disease biomarkers offers the potential to enhance the predictive validity of modern imaging with concomitant synovial pathobiological analysis further studies, integrating MRI with synovial tissue analysis, in well-controlled cohorts before and after therapeutic intervention are required in order to achieve this.

## **Figure Legends**

**Figure 1: PRISMA flow chart presenting the results of the search strategy**

**Figure 2: Assessment of RA joint abnormalities by magnetic resonance imaging.**

Coronal T1 weighted (A) image of wrist joint demonstrating extensive synovial thickening which enhances following administration of gadolinium (B). C. T2 fat suppressed coronal image demonstrating bone marrow oedema within the head of the proximal and base of the middle phalanx.. D. Axial T1 weighted image demonstrating erosions of bone cortex within 2<sup>nd</sup> and 3<sup>rd</sup> metacarpal heads E. Coronal T1 weighted image of metacarpal phalangeal (MCP) joints demonstrating significant joint space narrowing within second MCP joint

**Figure 3. Minimally invasive technique of ultrasound guided synovial biopsy of wrist joint.**

Inset depicts corresponding gray scale ultrasound image of biopsy needle inserted into wrist joint under extensor tendon complex

**Table 1.** The MEDLINE MeSH keyword search terms and Boolean operators  
1946-to present

**Table 2.** Summary of studies directly correlating MRI features with synovial  
pathobiology: MRI characteristics

*(DCE: dynamic contrast enhanced, SPP: suprapatellar pouch, Gd: gadolinium, RCT: randomized controlled trial, SQ: semi-quantitative, DMARD: disease modifying anti-rheumatic drug, ROI:region of interest, NA: not available, \*exact timing not specified)*

**Table 3.** Summary of studies directly correlating MRI features with synovial  
pathobiology: Histobiological characteristics

*(DCE: dynamic contrast enhanced, SQ: semi-quantitative, PMN: polymorphonuclear, DIA: digital image analysis, IHC: immunohistochemical, MRE: maximum rate of enhancement, VAS: visual analogue score, LL: lining layer, SL: sublining layer, qRT-PCR: quantitative reverse transcriptase PCR)*

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