
Article:
Humby, F, Mahto, A, Ahmed, M et al. (5 more authors) (2017) The Relationship Between Synovial Pathobiology and Magnetic Resonance Imaging Abnormalities in Rheumatoid Arthritis: A Systematic Review. Journal of Rheumatology, 44 (9). pp. 1311-1324. ISSN 0315-162X

https://doi.org/10.3899/jrheum.161314

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

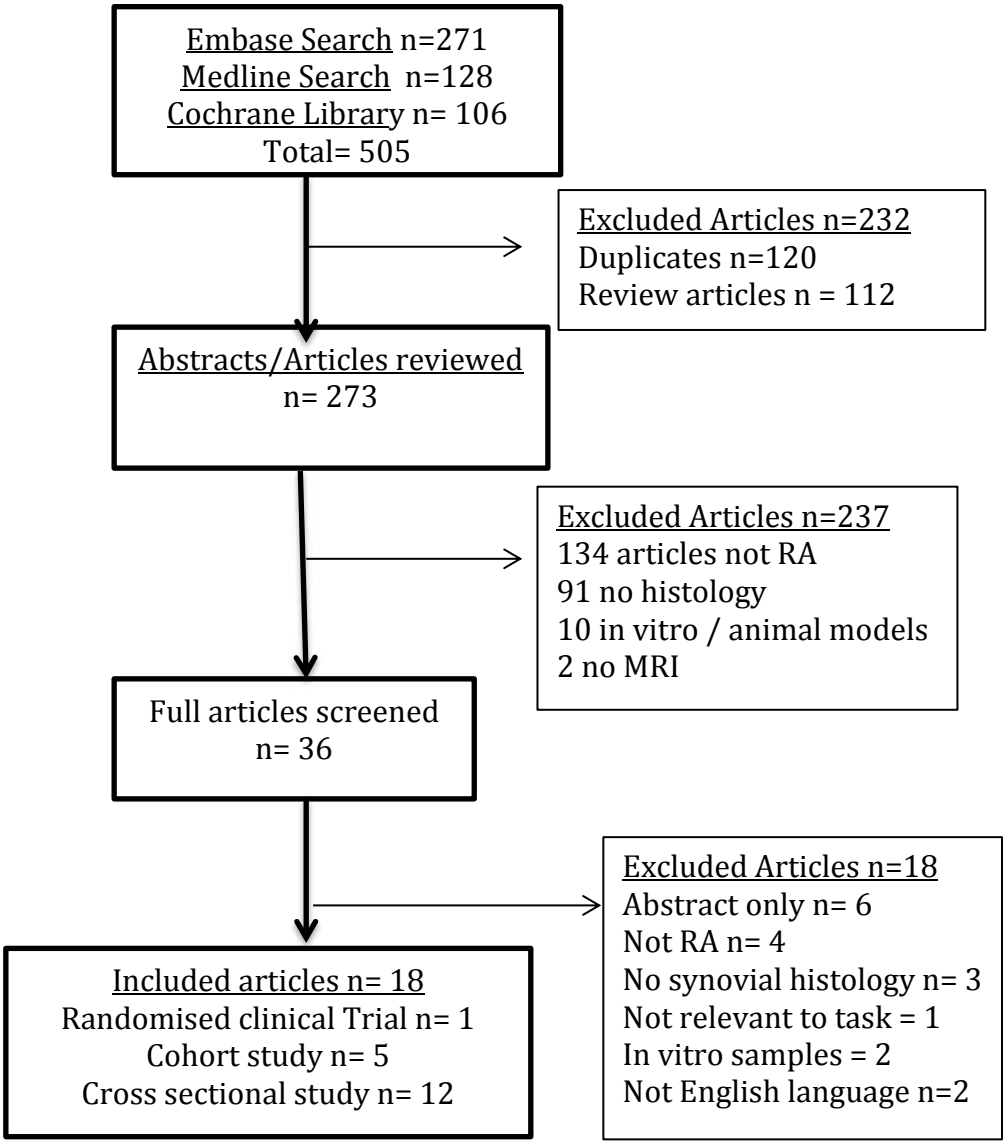

Figure 2. Assessment of RA joint abnormalities by magnetic resonance imaging.

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 2nd and 3rd metacarpal heads **E**. Coronal T1 weighted image of metacarpal phalangeal (MCP) joints demonstrating significant joint space narrowing within second MCP joint

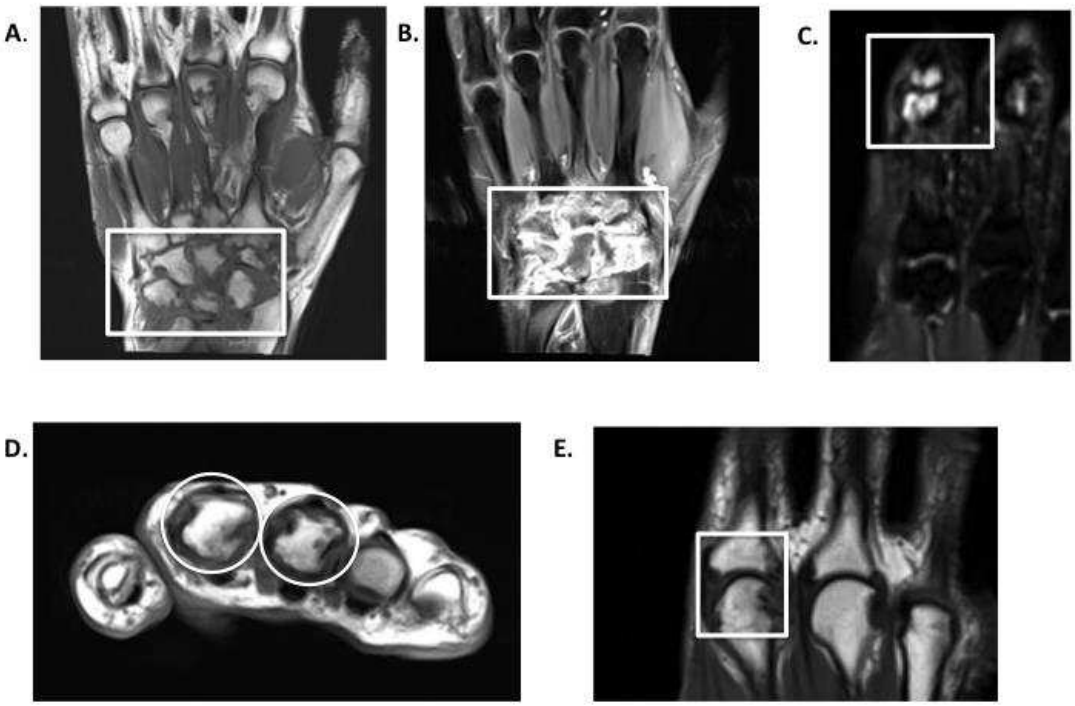

Figure 3. Minimally invasive technique of ultrasound guided synovial biopsy of wrist joint.

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

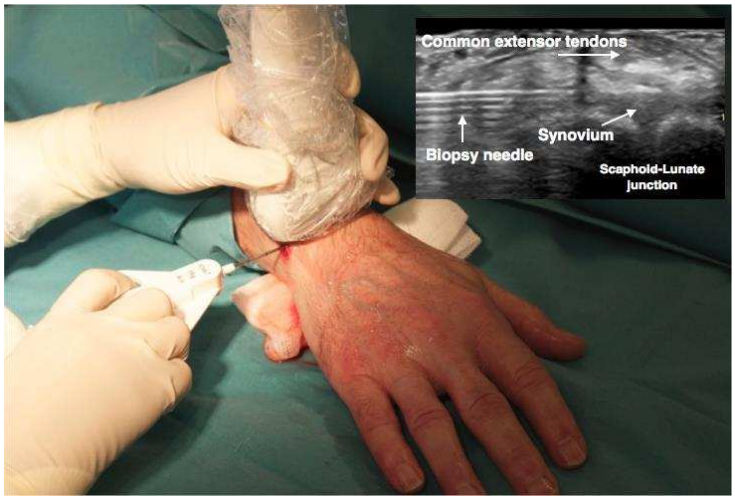
Common extensor tendons
Synovium
Biopsy needle
Scaphoid-Lunate junction

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

1	Exp *RHEUMATOID ARTHRITIS/	19	Exp*IMMUNOHISTOCHEMISTRY
2	(Rheumatoid AND arthritis).ti,ab	20	Pathol*. ti,ab
3	RA.ti,ab	21	Histo*.ti,ab
4	Rheumatoid.ti,ab	22	Immuno*.ti,ab
5	"inflammatory arthritis".ti,ab	23	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
6	1 OR 2 OR 3 OR 4 OR 5	24	Exp *JOINT SURGERY/
7	Exp *NUCLEAR MAGNETIC RESONANCE IMAGING/	25	Exp *ARTHROSCOPY
8	(magnetic AND resonance AND imaging).ti,ab	26	Exp*BIOPSY/
9	MRI.ti,ab	27	Exp*JOINT/
10	DCE.ti, ab	28	Surgery.ti,ab
11	(magnetic AND resonance AND imag*).ti,ab	29	Arthroscopy.ti,ab
12	7 OR 8 OR 9 OR 10 OR 11	30	Joint.ti,ab
13	6 AND 12	31	Biopsy.ti,ab
14	Exp *SYNOVITIS/	32	24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
15	Synovi*, ti.ab	33	16 AND 23 AND 32
16	14 OR 15	34	13 AND 33
17	Exp *PATHOLOGY/	34	[Limit to: Human and English Language]
18	Exp *HISTOPATHOLOGY/		

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)*

Study	Description	Early (E) vs established (Est) RA	Synovial Sampling Technique/joint sampled	Time from MRI to synovial sampling	Concomittant DMARD/steroid therapy controlled?	Joint assessed by MRI/biopsy site predetermined by MRI image?	MRI		
							Feature scored	Acquisition	Assessment
Konig et al (26)	**Case control cross sectional study** of 20 RA patients and 2 controls (OA). 8 patients with paired MRI and synovial tissue data. Main aim of study was to compare T1 and contrast enhanced T2 weighted MRI images with histological evidence of synovitis	Est	Arthroscopic and arthroplastic/knee	3 weeks	No/No	Knee/ yes	Synovial membrane, joint capsule, hyaline cartilage, subchondral bone marrow, juxtaarticular muscle tissue and pannus	1.5T+ contrast	DCE with ROI analysis
Tamai et al (17)	**Cross sectional study** of 9 RA patients. To clarify whether signal enhancement in dynamic MRI is dependent on the severity of pathologic	Est	Arthroplastic/knee	1-15 days	No/Intrarticular steroid for 3 months prior to study inclusion or during interval between MRI and	Knee/yes	Synovitis	1.5T+ contrast	DCE

	findings in the rheumatoid synovium.				arthroplasty was not permitted.				
Gaffney et al(20)	**Cross sectional study** of 21 RA patients to develop a method for quantifying acute synovial inflammation in RA utilizing MRI	Est	Blind needle biopsy/knee	Immediately prior*	No/No	Knee/No	Synovitis	0.5T +contrast	DCE
Gaffney et al(21)	**Cross sectional study** of 21 RA patients . To develop a quantitative technique for assessing synovial vascularity based upon contrast enhanced MRI	Est	Blind needle biopsy/knee	Immediately prior*	No/No	Knee/No	Synovitis	0.5T +contrast	DCE
Ostergaard et al (18)	**Cross sectional study** of 17 RA and 25 OA joints. To evaluate the relationship between synovial membrane and joint effusion volumes determined	Est	Arthroscopic or arthroplastic/knee	1-25 days	No/No	Knee/yes	Synovial volume	1.5T+contrast	Static (quantitative assessment)

	by MRI and macroscopic and microscopic synovial pathologic findings in patients with RA and OA.								
Osterg aard et al (19)	**Cross sectional study** of 17 RA and 25 OA joints. To evaluate dynamic as well as static Gd-enhanced MRI as measures of synovial inflammation in arthritis, by comparison with macroscopic and microscopic synovial pathology.	Est	Arthroscopic or arthroplastic/kn ee	1-25 days	No/No	Knee/yes	Synovitis	1.5T+cont rast	Static (quantitative assessment) and DCE
Veale et al (33)	**Randomised controlled Trial** of 13 RA patients with active resistant knee synovitis randomised to intra articular injection of placebo, 0.4mg or 40mg of anti-CD4. Underwent MRI and baseline and day 42 synovial biopsy.	Est	Arthroscopic/kn ee	Same day	Yes/Yes (stable DMARDs/stero id doses for 3 months prior to study entry)	Knee/yes	Synovitis	1.5T+cont rast	DCE

Ostendorf et al (22)	**Cross sectional study** of 22 RA patients. Aim was to evaluate a MRI findings in the MCP joints of RA patients macroscopically using miniarthroscopy	Early (<1.5yr, 9 pts) + Est (13 pts)	Mini arthroscopy/MCP	24 hours	No/No	MCP/No	i)Synovial volume, ii)synovial activity, iii)effusion, iv) joint space narrowing, v)bony alterations, vi) tenosynovitis and vii)BME	1.5T +contrast	SQ assessment (0-3) of each of 7 MRI parameters
Takase et al (23)	**Cross sectional study** of 10 RA and 5 OA patients. To simultaneously examine US, MRI and histopathology of joint lesions in RA or OA patients who required knee joint arthroplasty	Est	Arthroplastic/knee	24hours	No/No	Knee/biopsy site determined by pre-operative US scan	Synovitis	1.5T + contrast	OMERACT-RAMRIS SQ (0-3)
Axelsen et al(24)	**Cross sectional study** of 17 RA patients.To determine whether DCE-MRI evaluated using semi-automatic image processing software can	Est	Arthroplastic/knee	0-25 days	No/No	Knee/yes	Synovitis	1.5T + contrast	DCE (semi-automatic quantification)

	accurately assess synovial inflammation in RA knee joints.								
Buch et al (29)	**Prospective cohort study (interventional open-label clinical trial)** of 16 TNFi resistant RA patients. MRI and synovial biopsy were performed at baseline and 16 weeks following iv abatacept therapy to determine the synovial effect of abatacept.	Est	Arthroscopic/knee	0-2 days	Yes /yes (stable doses of DMARDs 28 days prior to inclusion)/ low dose corticosteroids permitted).	Knee/No	Synovitis	1.5T+contrast	DCE
Kirkham et al(34)	**Prospective cohort Study** of 60 RA patients. To explain the wide variability in joint damage progression from measures of pathologic changes in the synovial membrane.	Early (34% <2yrs) + Est	Arthroscopic/knee	Baseline study assessments	No/No	2^{nd}-5^{th} MCP joints/No	Bone erosion	1.5T	OMERACT-RAMRIS MRI score

Vordenbäumen et al (27)	**Cross sectional Study** of 9 patients**.** The objective of the study was to analyse if MRI synovitis relates to histological signs of synovitis in small RA joints.	NA	Arthroscopic/MCP	Up to 1 week prior	Partial all patients on MTX (+ 6 patients on biologic)/NA	MCP2/No	Synovitis,	3T+ contrast	DCE
Vordenbäumen et al (31)	**Cross sectional study** of 10 patients to analyse whether synovial markers within a MCP joint reflect global disease activity measures in RA.	NA	Arthroscopic/MCP	Up to 1 week prior	Partial (all on MTX +/adalimumab)/NA	Dominant MCP/No	Synovitis/BME/erosion	3T+contrast (6 patients), 0.2T +contrast (4 patients)	RAMRIS
Anandarajah (28)	**Retrospective cohort study** of 15 patients recruited to examine whether RA patients who meet remission criteria manifest inflammatory synovitis. 7 patients included with paired MRI/synovial tissue	Est	Arthroplastic/knee, wrist, hip, elbow and thumb	1 to 4 months prior	No/No	Knee (5), wrist (5), Hip (2), elbow (2) and thumb (1), /No	Synovial proliferation, BME, effusion and erosion	1.5T + contrast	SQ score (0-3)
Paramarta et al (25)	**Cross sectional study** in 41 patients (20 RA, 13 SpA, 8 other) aimed to compare the presence	Early (<12 months)	Mini-arthroscopy/knee, ankle	Not reported	Yes/yes	Knee, ankle/No	Synovitis and enthesitis	1.5T +contrast	SQ score 0-3

	and extent of synovitis and enthesitis in early untreated SpA and RA by paired MRI and synovial histopathology.								
Kennedy et al (30)	**Prospective cohort study of 16 RA and 4 PsA patients.** The aim was to compare the effect of tumor necrosis factor blocking therapy on hypoxia in vivo, macroscopic and microscopic inflammation, and MRI parameters using sequential MRI and synovial biopsy	Est	Needle arthroscopy/knee	24-72hrs prior	No/no	Knee/No	Synovitis	1.5T +contrast	DCE SQ (0-3)
Maijer et al (32)	**Prospective cohort study of 47 early arthritis patients (14 RA, 22 unclassified, 6 SpA and 5 other** arthritidies) . The aim was to examine whether DCE-MRI can be used as an objective measureof synovial inflammation using	Early (<1 yr)	Arthroscopic	Not defined	DMARD naïve/not defined	Knee	Synovitis	1.5T+contrast	DCE (quantitative assessment using pharmoacokinetic modelling)

	pharmacokinetic modelling.								

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)

Study	No. of Biopsies	Macroscopic assessment of synovium	Routine H&E assessment	IHC analysis	Synovial Gene expression analysis	Main Conclusion
Konig et al (26)	8-12 from different locations	No	Graded into one of 3 groups: fibrous, slightly hypervascular, and hypervascular.	No	No	DCE MRI is able to distinguish joint effusion from hypervascular pannus and to grade the vascularity of synovitis (only descriptive statistics reported).
Tamai et al(17)	1 samples from each of 3 sites (total number not defined)	No	8 histological features assessed SQ (0-3) fibrin exudation, PMN cell infiltration, mononuclear cell infiltration, multiplication of synoviocyte lining layer, villous hyper- trophy of synovial surface, proliferation of blood vessels, formation of granulation tissue and fibrosis	No	No	The rate and degree of signal enhancement with dynamic imaging significantly correlated with histological inflammation ($p<0.05$, Mann Whitney U)
Gaffney et al(20)	Not defined	No	SQ histological score 0-3, 3 histological features PMN infiltration, fibrin and hyperaemia	No	No	The rate of synovial membrane enhancement correlated with histologic features of acute inflammation ($r=0.63$, $p<0.01$)
Gaffney et al(21)	Not defined	No	Not assessed	Endothelial cell marker (Qbend30) assessed by DIA	No	Gd-DTPA enhanced MRI correlates with histologically determined synovial vascularity ($r=0.55$, $p<0.02$)
Ostergaard et al (18)	4 biopsy sites (total number not defined)	SQ macroscopic assessment intra operatively (0-3)	9 features: subsynovial infiltration of PMN leukocytes, subsynovial infiltration of mononuclear leuco cytes, surface fibrin deposition, multiplication of the synovial lining, villous hypertrophy of synovial surface, proliferation of blood vessels, perivascular oedema, formation of granulation tissue and fibrosis (SQ score 0-3)	No	No	MRI-determined synovial volumes are correlated with synovial inflammatory activity ($r=0.55$, $p<0.001$)

Ostergaard et al (19)	4 biopsy sites (total number not defined)	No	As for (18)	No	No	The early enhancement rate of the total synovial membrane was significantly correlated with the histologic grade of synovial inflammatory activity (r=0.73, $p<10^{-7)}$
Veale et al (33)	1 biopsy from each site (total number not defined)	Hyperaemia (0–1), granulation (0–1) or villous hypertrophy (0–2) +overall impression of the synovial inflammation VAS 0-100mm	Lining layer hyperplasia (SQ 0-3)	T cells (CD3, CD4 (OKT4), CD8), B cells (CD20), macrophages (CD68) and MHC class II. SQ analysis 0-5	No	The most significant correlations were observed between the MRE at the SPP ROI and arthroscopic VAS for synovitis (r=0.77, p=0.003) and between the MRE and immunohistological CD4 score (r=0.70, p=0.11)
Ostendorf et al (22)	4-6 biopsies from 2 patients	6 parameters (extent of synovitis, synovial thickening, hyperemia, proliferation, vascularity, fibrosis) plus 1 item each for bony and cartilaginous changes (SQ assessment, 0-3)	Synovial hyperplasia, fibrosis, vascularity, lymphocyte and stromal cell infiltration, and fibrin deposition	No	No	Synovial enhancement on MRI correlated with mini arthroscopy findings of hyperaemia (p=0.0038), and vascularity (0.0058). Synovial thickening on mini arthroscopy was significantly associated with synovial proliferation on MRI (p=0.0063). No formal evaluation of micro histological associations reported.

Takase et al (23)	Not defined	No	Synovitis score (inflammatory cell infiltrates, synovial lining layer thickness + vascularity) SQ 0- 3	DIA IHC assessment of sublining macrophages (CD68), cell proliferation (Ki67) and neoangiogenesis (CD31)	No	MRI synovitis significantly correlated with total synovitis score (r=0.48, p<0.05) and inflammatory cell infiltrates (0.47, p<0.05)
Axelsen et al(24)	4 (total number not defined)	No	SQ Synovitis score (0-3, 9 histological features)	No	No	The initial rate of enhancement from the Quick ROI and the Precise ROI revealed high correlations with the grade of histological inflammation (r= 0.70, p <0.001 and r= 0.74, p <0.001, respectively).
Buch et al (29)	6	No	No	T cells (CD3, CD154, CD4), APC (CD80, CD86),B cells (CD20, CD79), synovial fibroblasts (CD55), intra cellular	qRT-PCR (IL-1, IL-6, MMP1, MMP3, IFNγ)	A significant correlation between MRI synovitis scores (initial rate of enhancement and maximum enhancement) and IFNγ was observed (r=0.63 and r=0.79 respectively).

				adhesion molecules (CD54), macrophages (CD68) and CD11b+ neutrophils, macro-phages and dendritic cells. SQ assessment (0-4) of all parameters in LL and SL		
Kirkham et al(34)	3-4 (total number not defined)	No	SQ analysis of lining layer thickness, vascularity, sublining fibrosis, and cellular infiltrates and patterns (perivascular, diffuse, or focal aggregates)	No	qRT-PCR IFNγ, TNFα, IL16, IL1β, IL17, RANKL and IL10	Histologic features had no relationship to damage progression. mRNA levels of IL-1β, TNFα, IL-17 and Il10 were predictive of joint damage progression (multivariate regression analysis, r^2=0.57).
Vordenbäumen et al(27)	6 biopsies	Limited to direction of biopsies	Krenn score (51)	Sublining CD68 score	No	Maximum enhancement of the MCP significantly correlated with sublining CD68 staining (r = 0.750, P = 0.02) and Synovitis Score (r = 0.743, P = 0.02)

Vordenbäumen (31)	6 biopsies	No	Krenn score (51)	Sublining CD68 score, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF-1α)	No	VEGF staining correlated with BME (r=0.676, p=0.032) and erosion scores (r=0.695, p=0.026) of RAMRIS.
Anandarajah et al (28)	NA	No	Krenn score (51)(modified)	No	No	There was no statistical correlation between synovial scores on MRI and synovial hyperplasia on histology,
Paramarta et al (25)	Assume 6 biopsies	No	No	CD3, CD22, CD68, CD163, vwf	No	Significant association between MRI synovitis and CD68+ sublining macrophage number in RA/SpA (R=0.686, p=0.001)
Kennedy et al (30)	NA	Synovitis and vascularity (VAS 0-100mm)	Not reported	CD3, CD68, CD4, CD8, CD20, CD19 and factor VIII/αSMA	No	The change in MRI score after TNF blocking therapy was significantly associated with changes in macroscopic synovitis (P=0.056), sublining CD68 (p<0.002) and sublining CD4 cell number (p=0.032).

Maijer et al (32)	6 biopsies	No	No	vWF	No	This study demonstrates that the DCE-MRI pharmacokinetic parameters differe between different diagnostic categories and correlate with local (synovial vWF) and systemic markers of disease activity.