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MRI of Synovitis and Joint Fluid

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Abstract

Synovitis and joint effusion are common manifestations of rheumatic disease and play an important role in the disease pathophysiology. Earlier detection and accurate assessment of synovial pathology can, therefore, facilitate appropriate clinical management and hence improve prognosis. Magnetic resonance imaging (MRI) allows unparalleled assessment of all joint structures and associated pathology. It has emerged as a powerful tool, which enables not only detection of synovitis and effusion, but also allows quantification, detailed characterization and noninvasive monitoring of synovial processes. The purpose of this article is to summarize the pathophysiology of synovitis and to review the role of qualitative, semi-quantitative and quantitative MRI in the assessment of synovitis and joint fluid. We also discuss the utility of MRI as an outcome measure to assess treatment response, particularly with respect to osteoarthritis (OA) and rheumatoid arthritis (RA). Emerging applications such as hybrid PET-MRI and molecular imaging are also briefly discussed.

Keywords

Synovitis; Effusion; MRI; Osteoarthritis; Rheumatoid Arthritis

INTRODUCTION

The synovial membrane of diarthrodial joints is implicated in the initiation and progression of a wide range of degenerative, inflammatory and crystalline arthropathies. Magnetic resonance imaging (MRI) allows unparalleled assessment of all joint structures including the synovium, cartilage, and bone marrow amongst other articular structures (1). It allows noninvasive assessment of synovial volume, as well as active inflammation (assessed via increased vascularity detected with dynamic contrast-enhanced techniques).

International initiatives such as OMERACT (Outcome Measures in Rheumatology) and EULAR (European League Against Rheumatism) have emphasized standardization of MR assessment of synovial disease (2,3). The purpose of this article is to summarize the pathophysiology of synovitis and to review the role of qualitative, semi-quantitative and quantitative MRI in the assessment of synovitis and joint fluid. We also discuss the utility of MRI as an outcome measure to assess treatment response, particularly with respect to

osteoarthritis (OA) and rheumatoid arthritis (RA). Emerging applications such as hybrid PET-MRI and molecular imaging are also briefly discussed.

PATHOPHYSIOLOGY OF SYNOVITIS

Normal Synovial Structure and Composition

The synovium is a thin connective tissue, which lines diarthrodial joints and tendon sheaths. Its chief function includes production of synovial fluid to lubricate the joint, chemical homeostasis, and provision of nutrition for chondrocytes (4). The normal synovium is multilaminar with its thicker outer layer, the subintima, being rich in type I collagen but relatively acellular (5). The inner layer, called the intima, consists of a layer of 1-4 cells, predominantly macrophages and fibroblasts, with the latter reflecting the dominant cell population in the healthy synovium (5).

The Diseased Synovium

Diseases of the synovium can be broadly classified as those related to anatomical structures (e.g. plicae), degenerative inflammatory synovial proliferation (e.g. osteoarthritis), autoimmune inflammatory synovial proliferation (e.g. rheumatoid arthritis or juvenile idiopathic arthritis), infectious synovial proliferation (e.g. pyogenic or tuberculous), crystal deposition disease (gout or pseudogout) and reactive synovitis. In this review, we will focus on the most prevalent of these diseases, specifically osteoarthritis, and rheumatoid arthritis.

Synovial Changes in Osteoarthritis (OA)—There is increasing evidence that low-grade inflammation induced by a combination of trauma, metabolism, innate immunity and inflammatory factors contributes to the pathogenesis of OA(6,7). Cartilage breakdown is mediated by both chondrocyte and synovial macrophage-derived inflammatory mediators (8). Trauma is a known trigger of local inflammatory mediators, and there is increasing evidence that obesity also increases systemic low-grade inflammatory mediators (9). Innate immunity also likely plays a role in the pathogenesis of OA, with a study demonstrating compromised T and B cell immune function in OA patients, beyond that expected for age (10).

The synovium in OA is histologically characterized by thickening, hyperplasia, fibrosis and stromal vascularization (11). With immune activation, there is an influx of predominantly macrophages and T-cell lymphocytes, from the vascular compartment in response to cytokines and cell adhesion molecules (12) (13), with other contributing cells including synoviocytes and chondrocytes (14). Degradation of hyaline cartilage, subchondral bone, and other articular structures results in the release of inflammatory molecules, further promoting synovial inflammation. Synoviocytes produce pro-inflammatory mediators, which attract immune cells, promote angiogenesis and induce a phenotypic shift in chondrocytes (15). Chondrocytes produce additional cytokines and proteolytic enzymes causing a further increase in cartilage degradation and synovial inflammation (16). The diagram in Figure 1 depicts the processes involving the diseased synovium in OA and RA.

Synovial Changes in Rheumatoid Arthritis (RA)—Synovial proliferation is the hallmark of RA and is often seen early in the course of the disease. There is a progression to synovial pannus formation, periarticular bone demineralization, cartilage destruction and subchondral osseous erosions (17). Collagenase made at the synovial pannus-cartilage interface, is thought to be predominantly responsible for the erosions. Several other markers such as serum levels of immunoglobulin A (IgA), IgG and IgM rheumatoid factor (18), C-reactive protein (CRP) (1) and serum vascular endothelial growth factor (VEGF) (19) have also been shown to correlate with erosions on MRI (20).

Synovial Inflammation in Animal Models

Osteoarthritis—Post-traumatic OA models have shown synovial thickening and cellular infiltration to be the most frequent histological findings (21) (22). These changes occur rapidly, with synovitis most severe in the first two weeks after the insult (21,22). Noninvasive post-traumatic OA models have also shown that the severity of the synovial reaction may be related to the severity of the injury (23).

In an Anterior Cruciate Ligament (ACL) transection model, synovitis and cartilage erosions were reduced in CD4 deficient mice and slower progression of erosions was noticed in CD8 deficient mice. Anti-inflammatory approaches, for example, such as intra-articular IL-1Ra, to attenuate the acute phase have been tested in animal models and hold promise for prevention of OA, although the potential cessation of chronic inflammation and prevention of progressive structural change remains to be determined (24).

Rheumatoid Arthritis—There are several rodent models, which have significantly advanced the understanding of RA pathophysiology and contributed to advances in treatment (25). Animal models have also been used to identify optimal MRI contrast for evaluation of synovial pannus. In a rabbit knee model of synovitis, two gadolinium-based macromolecular intravascular contrast agents P792 (rapid clearance blood pool agent) and P717 (slow clearance blood pool agent) were compared to gadolinium-DOTA, a representative extracellular non-specific agent. While the high-molecular-weight P792 and P717 provided a progressive and persistent enhancement of arthritic synovial tissue, gadolinium-DOTA provided an early and rapidly declining enhancement with a concomitant diffusion in synovial fluid, therefore, limiting delineation of synovial pannus (26).

IMAGING OF SYNOVITIS AND JOINT EFFUSION

There is significant data to substantiate the use of MRI as a surrogate measure of histological synovitis (27) (28). Both dynamic MRI (27,29) and static MRI protocols (28) (30) have shown a correlation between MRI changes of synovitis and microscopic synovial inflammation assessed using hematoxylin and eosin (H&E) staining. Immunohistochemical analysis has also revealed a significant congruent relationship between MRI synovitis and CD4+ T cells (31), CD68+ sublining macrophage number (30) (29), cell proliferation (Ki67) and neoangiogenesis (CD31) (30). The consistent demonstration of a relationship between CD68+ sublining macrophage number and MRI synovitis is particularly significant as the only current synovial biomarker validated as a measure of disease activity (32). Correlation between MRI detected synovitis and degree of histological vascularity assessed through

semi-quantitative H&E stain evaluation (33), expression of endothelial cell marker QBend30 (34), and von Willebrand factor expression (35), has also been reported.

Signs of inflammation on MRI also correlate with the volume of joint effusion on arthrocentesis (36). Although effusion and synovitis often coexist, they are not synonymous (37). Joint effusion volume has been shown to correlate with microscopic synovial inflammation but not macroscopic inflammation (27). A contrast enhanced-MRI-based study showed that synovitis may be present with or without effusion (37). Also, in a cohort without radiographic OA, baseline joint effusion but not synovitis predicted the development of tibiofemoral cartilage loss (38). Thus, inflamed synovium and effusion should be regarded as two distinct entities.

Standardization, and Reliability in MRI Assessment of Synovial Disease

International initiatives such as OMERACT and EULAR aim to promote standardization and reliability (39) (2) with a consensus MRI definition of joint pathologies and a core of basic MRI sequences. The suggested MRI sequences include T₁-weighted imaging pre- and post-intravenous gadolinium contrast administration, T₂-weighted imaging with fat saturation or short TI inversion recovery (STIR) imaging in at least two planes or three-dimensional projections with a maximum slice thickness of 3 mm (40).

Based on multi-center studies, a semi-quantitative OMERACT rheumatoid MRI Scoring (RAMRIS) system has been developed for assessment of synovitis, bone erosions and bone marrow edema (BME) in RA wrists and hands (41). OMERACT published two atlases in 2005, standardizing RAMRIS and documenting expert-agreed features to be measured. A EULAR–OMERACT RA MRI reference image atlas was also developed to provide a standardized reference tool for the assessment of RA joints, allowing semi-quantitative scoring for inflammatory and destructive changes (3) thereby improving the consistency of MRI scoring among different centers and studies. Similarly, Juvenile Arthritis MRI score (JAMRIS) and Psoriatic Arthritis MRI score (PsAMRIS) systems have also been developed.

The OMERACT definition of synovitis on MRI is an area in the synovial compartment that shows above normal, post-gadolinium enhancement of a thickness greater than the width of the normal synovium.

The Role of MRI in the Assessment of the Synovium

Non-contrast MRI—The normal synovial tissue has an intermediate signal on T₁-weighted imaging and high signal on T₂-weighted imaging. A variety of approaches using non-contrast MRI for assessment of synovitis have been proposed. One study utilized two axial sequences: T₂-weighted sequence to assess synovial fluid and 3D spoiled gradient recalled (SPGR) sequence to assess the synovial membrane. The authors determined this technique to be accurate and reproducible, however, this remains untested against an established reference standard such as histology or contrast enhanced-MRI (42). Furthermore, differentiation between synovial fluid and thickening is not possible and it has been suggested that gradient echo-type sequences are particularly less suited for evaluation

of synovitis as they are prone to chemical shift artifacts that compromise assessment of synovial thickness and differentiation from other surrounding structures (43).

Non-Contrast versus Contrast-Enhanced MRI—Non-contrast MRI is overall a useful clinical tool and therefore is commonly used to assess synovitis (44). In the knee, hypointense signal alteration in the Hoffa's fat pad on non-contrast T₁-weighted spin-echo images (45) and hyperintense signal on fluid-sensitive sequences such as fat-suppressed proton density (PD) or fat-suppressed T₂ weighted spin-echo imaging sequences have been suggested as a surrogate marker for synovitis (44). However, there is increasing recognition of the limitations of non-contrast MRI in the assessment of synovitis.

Contrast-enhanced MRI is a more reliable measure of synovial inflammation, particularly in clinical trials as an outcome measure for therapeutic response. The most important advantage of contrast enhanced-MRI is that it allows differentiation between synovium and fluid (Figure 2). Inflamed synovium enhances after contrast administration, while an effusion usually does not enhance on static contrast-enhanced MRI. On non-contrast examinations, both synovium and effusion may be hyperintense on fluid-sensitive sequences (Figure 3). Roemer et al. compared fat saturated PD-weighted sequences and contrast-enhanced fat-saturated T₁-weighted sequences for assessment of patellofemoral synovitis in OA and found only fair to moderate agreement between these techniques. Signal alteration in the Hoffa's fat pad on non-contrast MRI was a sensitive (86–97%) but not a specific (10–38%) sign of synovitis (46). Loeuille et al. compared three MRI scoring systems for evaluating synovitis and joint effusion finding only contrast-enhanced MRI to correlate with microscopically proven synovitis, and no correlation with microscopic synovitis observed on non-contrast MRI (47).

Contrast-enhanced MRI detected synovitis has been shown to correlate with histology (48) and is more sensitive (49) and specific (46) than non-contrast MRI. Two large studies found a significant correlation between contrast-enhanced MRI-detected synovitis and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score (50) (51), whereas a smaller study found no such correlation (52). These conflicting findings may be attributable to a much smaller sample size of the latter (400 compared to 20). Additionally, deviations in the synovitis scoring methods utilized by various investigators make a direct comparison of studies difficult. A reliable and validated scoring system, using contrast enhanced-MRI, such as presented by Guermazi et al. (51) may be useful for standardized evaluation of synovitis.

Static versus dynamic contrast-enhanced MRI

Static contrast-enhanced MRI—In static contrast-enhanced (SCE) MRI, images are acquired in one or two planes pre- and post-enhancement. In dynamic contrast-enhanced (DCE) MRI, T₁-weighted volume acquisitions, are repeated over the same anatomical areas beginning at the time of injection and for several minutes thereafter, thus enabling evaluation of the dynamics of synovial enhancement (53).

After intravenous injection, gadolinium passes into the interstitial space at a rate dependent on local capillary permeability and tissue perfusion, which is increased during inflammation.

SCE-MRI protocols assess the volume of enhancing synovitis at a fixed time point. Synovial volume can be quantified via manual or semi-automated segmentation of the synovial tissue. Static images can also be assessed using the validated semi-quantitative OMERACT-RAMRIS score (40).

Limitations of static contrast-enhanced imaging—Inflamed synovium enhances immediately, after which gadolinium-DTPA rapidly diffuses to the adjacent joint fluid (54). This can blur the margins of the synovium, leading to an overestimation of synovial volume. Early image acquisition following the administration of intravenous gadolinium may minimize this issue, however optimal timing for quantification of synovial volume remains to be established. The timing of the acquisition suggested in the literature vary widely; from few seconds post-injection (55) to within the initial 10 min (56). It has been suggested that waiting as long as 10 minutes can be problematic and therefore one should aim to image within 5 minutes.

Dynamic contrast-enhanced MRI—DCE-MRI involves the rapid acquisition of sequential images during and after administration of contrast and assesses the rate of enhancement of the synovial tissue. Results can be influenced by factors such as synovial perfusion and capillary permeability and more sensitively reflect local synovial inflammatory activity (57). Studies have shown that early enhancement reflecting the initial distribution of gadolinium, accurately reflects the inflammatory activity of the joint. The signal intensity of joint effusions also increases, starting in the periphery and subsequently gradually approaching the central parts, as gadolinium passes into the joint space by diffusion of fluid from synovial capillaries (53) (27). Thus, the extent of synovial enhancement may be misinterpreted, if the assessment is performed only on a static contrast enhanced-MRI acquired during a late phase.

DCE-MRI is a useful tool for assessing synovitis in RA and OA patients (53). Kirkhus et al. showed that DCE MRI proved useful in differentiating synovitis in hand OA from that in RA (58). Ostergaard et al. reported that the omission of intravenous gadolinium led to decreased reliability in the assessment of RA synovitis (59), therefore they recommend the use of gadolinium for comprehensive assessment of synovitis, especially when synovitis is the focus of interest as a surrogate outcome measure or as a predictor of subsequent clinical or structural changes. A study by Riis et al. investigated the association between pain and peripatellar-synovitis. Synovitis was assessed in the peripatellar recesses with (1) DCE-MRI, using both pharmacokinetic and heuristic analytical models, (2) SCE-MRI, and (3) non-contrast MRI, and correlated with pain assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The study reported statistically significant correlations between pain assessed using KOOS and all but one of the MRI variables. Overall, DCE-MRI showed a stronger correlation with pain compared to SCE-MRI (60).

Quantitative analysis using dynamic contrast-enhanced MRI—DCE-MRI can quantify both the amount of synovium and joint fluid in arthritic joints and provide objective information regarding the severity of inflammation. Rapid serial T₁-weighted images at different time intervals following a contrast bolus, demonstrating an S-shaped curve of intensity against time is typical of inflamed synovium (61). The 'E-ratio' has been suggested

as a measure of synovitis, derived by dividing the rate of increasing synovial enhancement post contrast injection by the baseline signal intensity of the synovial membrane. Significant correlation between the E-ratio and biopsy appearances of synovitis has been identified (61). Gaffney et al. re-assessed the calculations used to measure synovitis in 21 patients with knee synovitis, suggesting that the initial rate of synovial enhancement be used as an absolute measure rather than relative to a potentially highly variable baseline (62). The magnitude and rate of synovial enhancement on sequential MRI following bolus intravenous gadolinium injection have been demonstrated to correlate with the histological severity of synovial inflammation and also with disease activity clinical markers (63) (64). The proposed optimum time for measurement of enhancement is 30 seconds to 1 minute post Gadolinium-DTPA injection, as the maximum correlation coefficients to histological inflammation were identified in this period (63). Despite this, moderate and severe inflammation on histology cannot be differentiated with MRI (63).

Factors in dynamic contrast-enhanced MRI—For DCE to become commonplace in clinical practice, protocols need to be standardized and the image analysis needs to be fully automated. The optimal protocol for DCE-MRI is yet to be established. This would require addressing several variables including which part of the joint to image, what plane to use, how to manage the intrinsic heterogeneity of inflammation in the synovial compartment and which variable of enhancement to use (64). One study comparing a manual outline method and automated data analysis of DCE-MRI found the 2 methods to be comparable (65).

MRI assessment of synovial volume

MRI based volumetric measurement of enhancing tissue can be performed using both manual and computer-aided segmentation and processing techniques (66) (57). Studies have found the synovial volume to correlate with joint swelling and tenderness (67). Histopathological analysis has also shown a relationship between synovial membrane volumes and synovial inflammatory activity (66). Ostergaard et al. reported a decrease in contrast-enhanced MRI assessed synovial volume in the wrists of RA patients after therapy with disease-modifying antirheumatic drugs (DMARD) and prednisolone.

The prognostic value of pre-treatment synovial volumes is well documented; the rate of erosive progression is correlated with baseline synovial membrane volumes (64). Using a combined score for synovial thickening and synovial enhancement has been shown to be more predictive of bone erosions than only synovial enhancement score used alone (64). Even unenhanced synovial volumes analyzed in the finger, including active and inactive synovial tissue, effusion and fibrous tissue, have been found to be predictive of bone erosion on follow-up imaging after 1 year (67).

MRI assessment and Semi-quantitative scoring systems in OA

Neogi et al. assessed non-contrast knee MRI in over a thousand patients with OA. They found synovitis in 60% of this population and effusion in 66% (68). Contrast-enhanced MRI detected synovitis has been found to be strongly correlated with radiographic OA severity and reported in 74% of patients exhibiting all grades of OA severity (69), and in 95% of patients with predominantly moderate to severe radiographic OA (50). There is increasing

evidence that synovitis may be independently associated with the progression of OA. Studies have shown that even after adjustment for other structural pathologies known to cause synovitis, synovitis remained associated with incident radiographic OA and demonstrated a graded association with radiographic progression (70,71). In another study of knees without MRI defined cartilage damage or radiographic OA, the presence of effusion or synovitis was associated with a significantly increased risk of cartilage loss (38).

Three well established semi-quantitative scoring systems for MRI assessment of knee OA all include evaluation of synovitis: the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (72), Boston Leeds Osteoarthritis Knee Score (BLOKS) (73), and Knee Osteoarthritis Scoring System (KOSS) (74). In the relatively recently introduced MRI Osteoarthritis Knee Score (MOAKS), synovitis is also graded semi-quantitatively on a Likert-scale as follows: 0 = normal or physiological, 1 = mild or small, 2 = moderate or medium, and 3 = severe or large (6). A study by Rhodes et al. (57) demonstrated that semi-quantitative scoring of OA synovitis using contrast-enhanced T₁-weighted imaging correlated well with manual volume assessments.

To better localize contrast-enhanced MRI detected knee synovitis, an alternative scoring system has been presented (75), whereby synovitis is graded from 0 to 2 at 11 different locations in the knee joint: medial and lateral parapatellar recess; suprapatellar, infrapatellar, intercondylar, medial and lateral perimeniscal regions; and adjacent to posterior and anterior cruciate ligaments, loose bodies, and Baker's cysts. This scoring system was found to have good to excellent inter-reader and intra-reader reliability for assessment of whole-knee synovitis. In this study, moderate to severe synovitis showed a significant association with the maximum Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score when compared with knees with no or equivocal synovitis. Using this scoring method, the same investigators also reported that whole knee synovitis as semi-quantitatively assessed on contrast enhanced-MRI was strongly associated with tibiofemoral radiographic OA and severe meniscal damage (69,76).

MRI assessment and semi-quantitative scoring schemes in RA

Although the inciting pathological events in RA have been historically believed to reflect primarily synovitis leading to osteitis, cartilage wear, and ultimately osseous erosions, the process is likely more complex and incompletely understood. A significant relationship between synovitis and BME (77), as well as between synovitis and the development of erosions has been demonstrated (78). The precise contribution of synovitis in initiating and sustaining bone erosions, however, needs further study. Studies using MRI have identified BME and erosions as relatively early events, with cartilage loss occurring later (79) in the course of the disease. MRI studies have also demonstrated an association between BME, synovitis, baseline cartilage damage and subsequent cartilage loss (80). MRI can show changes of early synovitis, reactive osteitis and has the capacity to detect bone erosions up to two years earlier than radiographs (81). These findings are particularly significant, given the improved treatment algorithms for RA (1) (82). Additionally, they support the use of MRI as a robust outcome measure in clinical trials of future therapeutic agents.

Rheumatoid Arthritis MRI score (RAMRIS)—RAMRIS is a standardized MRI based semi-quantitative scoring system for RA, which is continually updated during the OMERACT methods development conferences (83). The scoring system focuses on the inflammatory soft tissue and destructive bone alteration and has been extensively utilized as an outcome measure, particularly in studies focusing on the hands and wrists. Using this scheme, synovial soft tissue thickening manifesting as an increased volume on the T₁-weighted image and increased water content manifesting as high signal on fat-suppressed T₂-weighted imaging is assessed in three wrist regions (distal radioulnar, radiocarpal, intercarpal joints) of the dominant or most inflamed wrist. For the hand, it is evaluated in 2nd through 5th metacarpophalangeal joints of the dominant or most inflamed side (84). A systemic review by Woodworth et al, which focused on published literature spanning 1970 through June 2014, found 1.5T MRI based RAMRIS detected synovitis, osteitis, and erosions to be valid and useful for evaluating joint inflammation and damage in RA involving the wrist and hand (84).

Some studies have suggested that signs of joint inflammation in the foot on MRI are as prevalent as in the hand and may even be present in the absence of inflammatory MRI findings of the hand. Sewerin et al. found that a combined hand and foot MRI score identified patients with continuing disease activity that would have been missed by consideration of the traditional RAMRIS alone (85).

MRI Based Monitoring of Treatment Response

Monitoring of treatment response has generally focused on assessment of synovial volume or quality as assessed by its vascularity.

Osteoarthritis—The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections supports therapeutic targeting of the inflammatory process in OA. Using DCE-MRI in knee OA patients before and 1-2 weeks after intra-articular injection of 80 mg methylprednisolone, Gait et al. found DCE-MRI derived measures of synovial enhancement to be more sensitive to treatment response and more strongly associated with changes in pain than static assessment of synovial volume (86).

Rheumatoid Arthritis—The treatment goal in RA consists of DMARDs with or without concomitant corticosteroid therapy, with early initiation of therapy being vital to successful management. Methotrexate (MTX), is the standard therapy, but the remission rate for MTX treatment is <65%. The biological antirheumatic drugs are expensive and usually reserved for use if the conventional DMARDs are ineffective or contraindicated. These drugs targeting inflammatory cytokines, such as tumor necrosis factor α (TNF- α) or interleukin 6 (IL-6) via the IL-6 receptor (IL-6R), have expanded the treatment options for patients with RA. The combination of methotrexate and infliximab (an anti-TNF- α agent) for example has been found to be superior to methotrexate alone for reducing MRI-detected signs of synovitis and BME in patients with early RA (87).

A randomized clinical trial that used DCE-MRI to detect synovial enhancement at baseline and four months of treatment with leflunomide or methotrexate found a statistically significant difference between the two treatment groups using DCE-MRI, while clinical

assessment failed to detect changes (88). The histological findings from synovial biopsies of the same joints however corresponded closely with the MRI findings and regions of interest used for dynamic contrast-enhanced MRI curve generation were matched to the biopsy sites at arthroscopy (89). Another open-label placebo-controlled study of intraarticular anti-CD4 (31) reported a significant correlation between MRI synovitis and microscopic synovitis with a trend toward improvement in both histological and MRI synovitis only in patients receiving active treatment. A different study investigated the effect of TNF inhibitor therapy on synovitis assessed via DEC-MRI and arthroscopic synovial biopsy (90). The authors reported a significant relationship between macroscopic synovitis/vascularity and MRI detected synovitis. They also reported an association between the decline in CD4+ T cells, CD68+ sublining macrophages and synovitis on MRI.

Advanced MRI techniques for monitoring drug treatment

T1rho mapping is an advanced research MRI technique that has been used to study collagen/proteoglycan matrix changes in articular cartilage (91). Ku and colleagues evaluated the feasibility of MR T1rho in assessing radiocarpal cartilage matrix changes following RA treatment with certolizumab, an anti-TNF biologic drug. They identified significant correlations between changes in radiocarpal T1rho and changes in disease activity as assessed by clinical and patient-reported outcomes. There is a large potential role for compositional techniques such as T1rho (Figure 4) and T₂ mapping amongst others, in the assessment of RA disease activity and treatment response (91).

Magnetic Field Strength In The Assessment Of Synovitis

The use of low field strength extremity MRI scanners has increasingly become commonplace amongst rheumatologists and other healthcare practitioners. Several studies have compared these low field strength MRI scanners with higher field strength magnets (92) (93). Ejbjerg et al. compared a 0.2T with a 1.0T MRI scanner and found the mean sensitivity, specificity, accuracy, and ICC of low-field MRI for detection of synovitis, where high-field MRI was considered the reference standard, to be 90%, 96%, 94%, and 0.923 (P < 0.05), respectively (93). It is noteworthy that Ejbjerg et al. found the overall sensitivity for detection of BME on the low-field scanner was only 39%, which may limit the usefulness of this type of scanner in RA since BME has been proposed to be a pathological event of major prognostic significance (67) (94). Lindegaard et al. demonstrated that low-field-strength extremity systems are superior to clinical examination for the detection of synovitis (95). Additional work is required to assess the reproducibility of results using low-field MRI units and inter-scanner reproducibility for DCE-MRI synovitis.

MRI Assessment of the Synovium in the Pediatric Population

There is particular interest in the utility of MRI in the assessment of juvenile idiopathic arthropathy (JIA) patients. Nusman et al. compared contrast-enhanced MRI detected synovitis in a group of clinically active JIA patients with a normal control group using the Juvenile Arthritis MRI Scoring system (JAMRIS) score. They found enhancing synovium (> 2 mm) to be present in 52 % of unaffected children and overall no difference between the 2 groups using the total JAMRIS score for synovitis. The authors concluded that mild

synovial thickening is commonly present in children unaffected by JIA and that infrapatellar and cruciate ligament synovial involvement were more specific for JIA (96).

Hemke et al. attempted to define the contrast-enhanced MRI standards for the normal pediatric knee, using JAMRIS. The overall mean thickness of the normal synovial membrane was 0.4 mm (range, 0.0–1.8mm), with the synovium being most thick around the cruciate ligaments, and in the retropatellar and suprapatellar regions. The mean overall diameter of the largest pocket of joint fluid was 2.8 mm (min-max; 0.9–8.0mm). The investigators concluded that the JAMRIS cut-off value of 2 mm might be considered a valid measure for evaluating synovial hypertrophy (97).

MRI Assessment of Synovitis After Arthroplasty

MRI is increasingly being used in the clinical setting to investigate joint pain following arthroplasty. The presence of lamellated hyperintense synovitis on MRI of knee arthroplasty has a high sensitivity and specificity for infection (98). Diagnostic accuracy of MRI has been reported to differ between index and revision total knee arthroplasty (TKA). A study by Li et al., utilizing surgical pathology and microbiology as a reference, found that MRI could distinguish between particle-induced synovitis, infection, and nonspecific synovitis, with almost perfect reliability and diagnostic accuracy, which was higher for index TKA than for a revision TKA (99).

MRI Assessment Of Other Miscellaneous Synovial Diseases

Psoriatic arthritis (PA)—Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease, which is histologically characterized by less pronounced hyperplasia of the intimal lining layer, marked vascularity, and a synovial infiltrate composed of B cells, plasma cells, dendritic cells, CD 163+ macrophages, larger influx of neutrophils, and fewer synovial T cells compared to RA.

The OMERACT Psoriatic Arthritis MRI Score (PsAMRIS) has been developed as a tool for MRI assessment of hands and feet in PsA clinical trials. This scoring system has shown overall good intra-reader agreement in the hand and foot and has been found to be responsive to change over time (100). A recent study found that MRI of the feet may demonstrate subclinical inflammatory joint disease in psoriasis patients without clinically evident arthritis (101).

Gout—Gout is a crystalline arthropathy characterized by deposition of monosodium urate (MSU) crystals in soft tissues and joints due to hyperuricemia. The deposition of MSU crystals incite a synovial inflammatory process and arthropathy as well as causing a formation of gout tophi, which are foreign body granulomas that include macrophages and MSU crystals. Chronic arthropathy develops after several years of recurring acute arthritis attacks. Thus, chronic gout arthritis generally affects older patients. The first metatarsophalangeal joints and knees are the most frequently affected (Figure 5).

Pigmented villonodular synovitis (PVNS)—PVNS is a form of villonodular proliferation of the synovium with hemosiderin pigment deposition, which may develop in

the bursa and tendon sheaths. The most common type of intraarticular PVNS is the diffuse form, but a localized form of PVNS may rarely be encountered. MRI reveals prominent diffuse villous or nodular proliferation of synovium and associated joint effusion. Synovial thickening is visualized as increased girth and intermediate to low signal intensity of the synovium on T₁-weighted imaging. There are hypointense areas on T₂-weighted imaging due to hemosiderin which also causes blooming artifacts on gradient echo sequences because of its magnetic susceptibility, almost pathognomonic in all forms of PVNS. These lesions also show enhancement after intravenous contrast administration.

Lipoma arborescens—Lipoma arborescens is a rare idiopathic disorder most frequently affecting the knee joint and characterized by villous lipomatous proliferation of the synovium. MRI exhibits synovial proliferation with frond-like fatty content, which has similar signal intensity to subcutaneous fat on all sequences and shows suppression on fat-saturated images.

MRI versus Ultrasound (US) in Assessment of Synovitis

Ultrasound has been recommended for diagnosing and monitoring disease activity in RA, evaluating subclinical synovitis and detecting disease progression (102). The presence of inflammation detected on US, as with MRI, can be used to predict the progression from undifferentiated inflammatory arthritis to clinical RA (103) (Figure 6). A recent systematic review which used MRI as a reference standard found US to be a valid and reproducible technique for assessment of synovitis in the wrist, metacarpophalangeal, proximal interphalangeal and knee joints (104). MRI does have several important advantages, however. It can visualize synovium located deep within the joint and is less susceptible to patient body habitus. Furthermore, MRI can detect additional BME lesions suggestive of osteitis, whereas US cannot. Volumetric measurements of synovium are also difficult with US.

Hybrid PET-MRI

Positron emission tomography (PET) provides quantitative information about molecular and physiologic changes that often precede structural and biochemical changes within the synovium. PET-MRI systems potentially represent a new complete integrated imaging tool for the diagnosis and assessment of synovial disease, in the form of both the high-resolution morphologic detail of the synovium and contrast enhancement patterns in conjunction with metabolic information. Higher FDG activity has been shown to correlate with intra-articular derangement, with the maximum standardized uptake value (SUV_{max}) significantly associated with cartilage loss, the degree of synovitis and meniscal tearing on MRI (105). MRI PET also allows localization of active synovitis for example within the intercondylar notch, which may represent the most metabolically active region of the knee (105) (Figure 7).

Although technical considerations require further innovation and improvement for accurate and optimized PET-MRI protocols, there appears to be a scientific drive to resolve these limitations. However, in order to be incorporated into widespread routine practice, PET-MRI

will need to demonstrate sufficient clinical benefit to justify the additional cost and complexity.

MRI Based Molecular Imaging using Contrast Agents

Molecular imaging of inflammation is a rapidly growing specialty with multiple potential applications. The range of molecular targets continues to expand and MRI-based molecular imaging will gain momentum with the advent of new magnetic nanoparticles that can be adapted for specific targets.

Accumulating magnetic nanoparticles cause shortening of the MRI T_2 and T_2^* relaxation times of the surrounding tissues, which causes a signal reduction (negative contrast). Monocytes and macrophages have been targeted in the setting of inflammation using a variety of nanomaterials, such as the small paramagnetic iron oxide nanoparticles (SPIO) and ultra-small paramagnetic iron oxide nanoparticles (USPIO). Studies have shown that accumulation of USPIOs in experimental septic arthritis allows the identification of early synovitis and therapy monitoring (106).

Nuclear medicine techniques may also be fused with MR imaging to improve assessment of synovitis. Kraus and colleagues demonstrated direct in vivo evidence of activated macrophages in human OA. Through binding to folate receptor- β (FR- β), the new (99m) Tc-EC20 (Etarfolatide) imaging technique was found to detect activated, but not resting, macrophages in vivo. The quantity of knee-related macrophages was significantly associated with knee pain severity and radiographic knee OA severity including joint space narrowing and osteophytosis. Macrophages were also localized to joints commonly affected by OA including hand finger joints (12%), thumb bases (28%), shoulders (26%), great toes (18%) and ankles (12%). The presence of joint pain at fingers, wrists, ankles and great toes was significantly positively associated with the presence of activated macrophages at these sites. This study provided the first direct in vivo evidence for macrophage involvement in OA in a substantial proportion of human knees (Figure 8)(107). Fusion of these images with the morphological images obtained via MRI may increase sensitivity and specificity for active synovitis.

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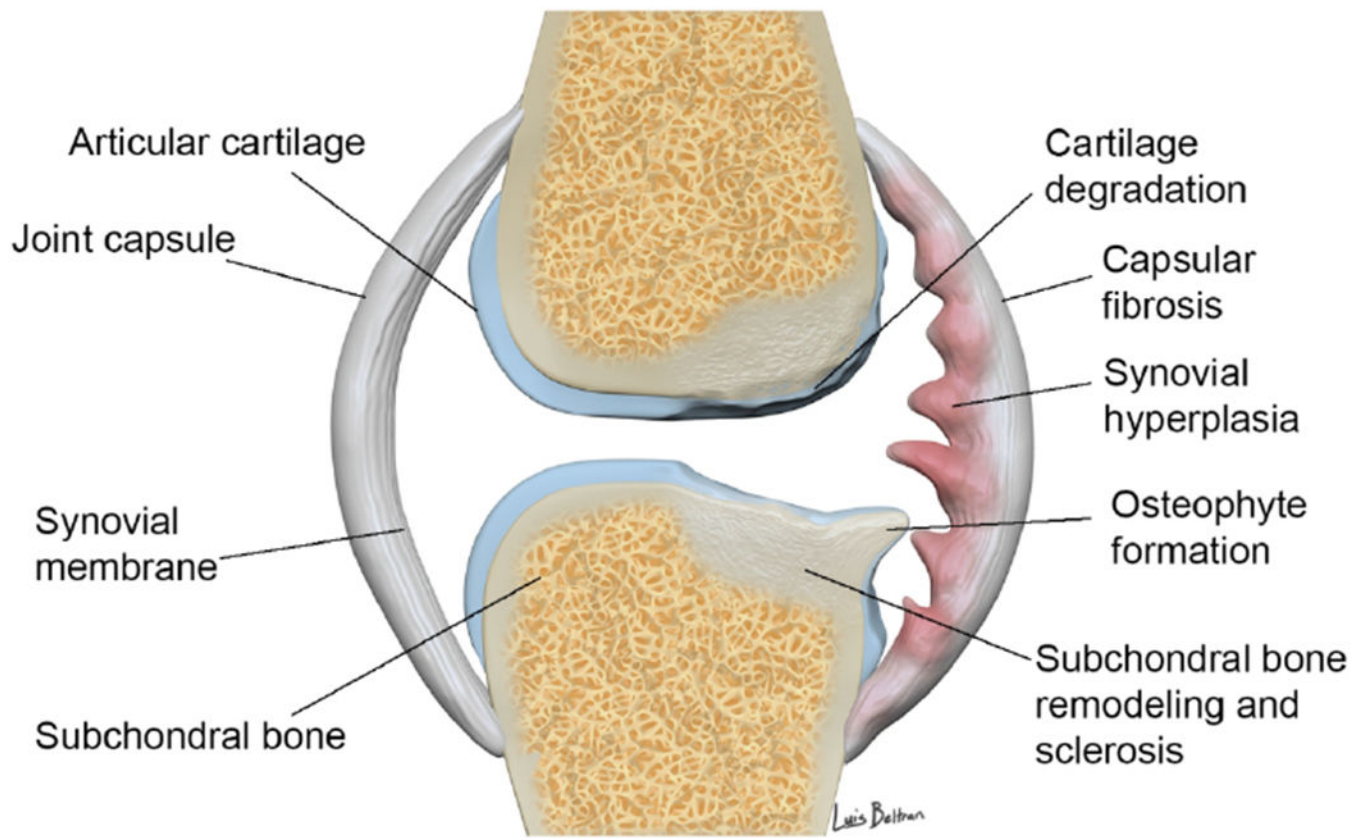
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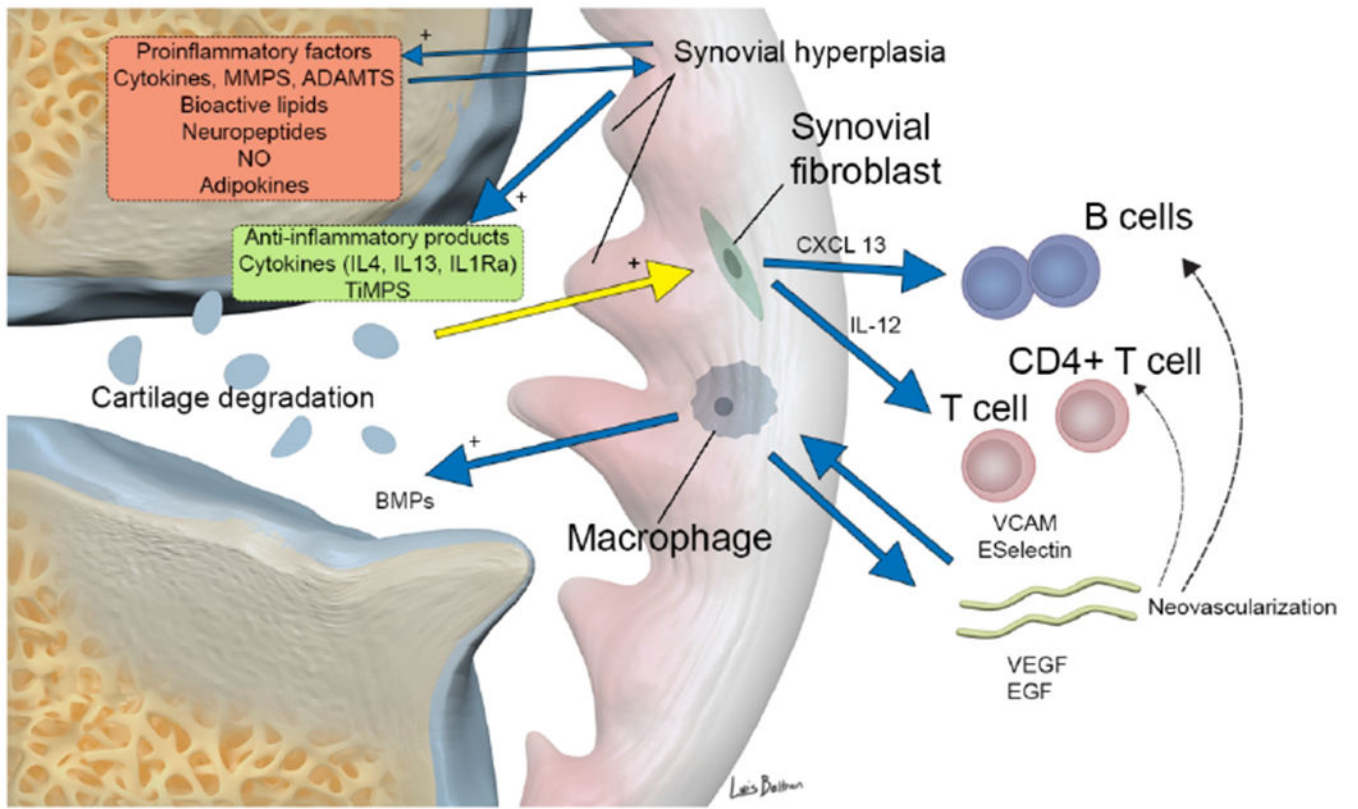
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Summary

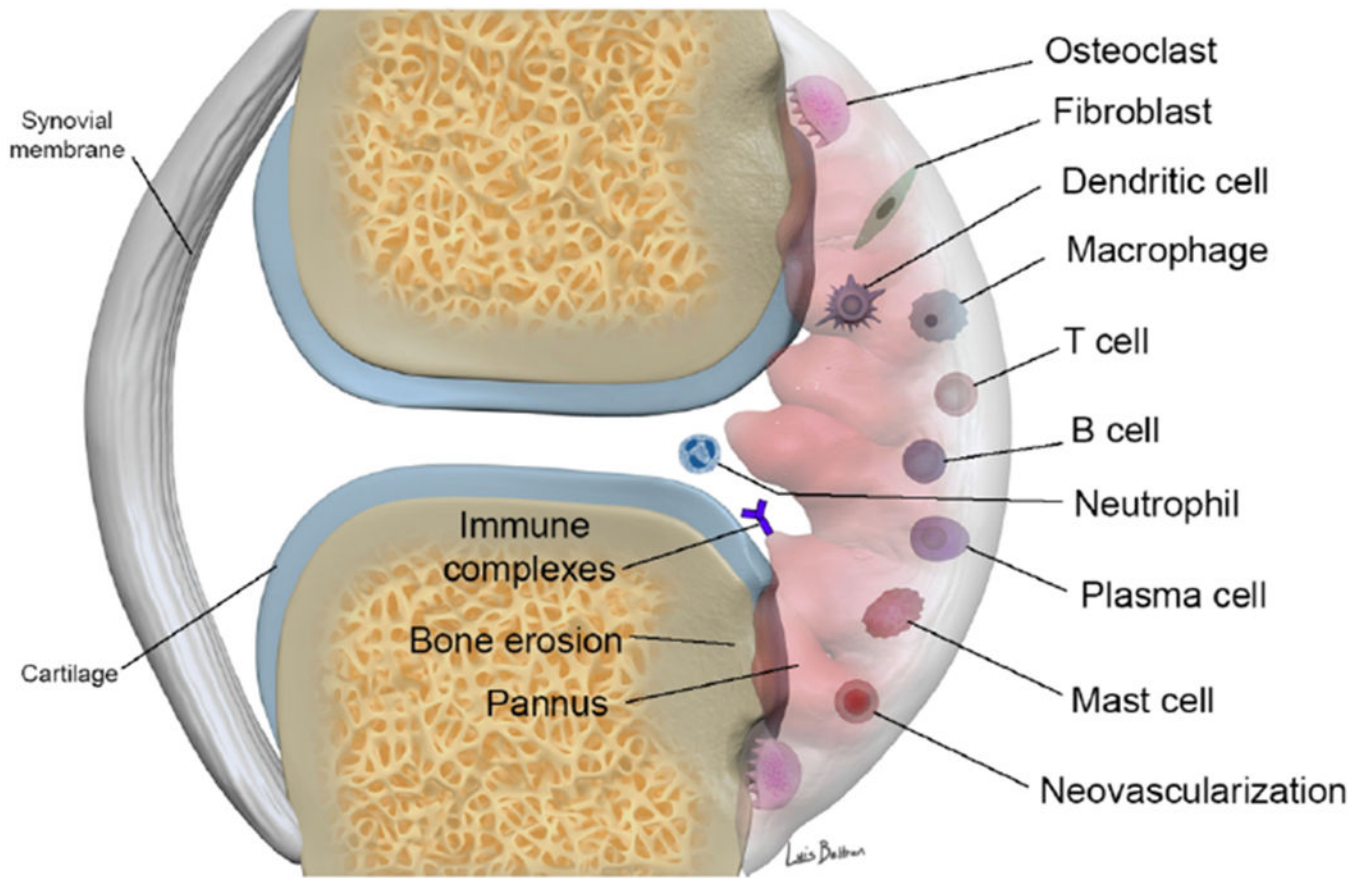
MRI provides an unparalleled non-invasive assessment of synovitis and may serve as a robust outcome measure in clinical trials of pharmaceutical therapies for the rheumatic diseases. With the advent of new therapies capable of preventing joint destruction, there is increased emphasis on MRI for early diagnostic and prognostic imaging as well as disease monitoring. Several semi-quantitative scores have been established for this purpose, which may have applications in the clinical settings. The continual advancement of MRI techniques and the advent of new hybrid-MRI imaging modalities such as PET-MRI hold promise in further improving the assessment of synovial disease.



a



b



c

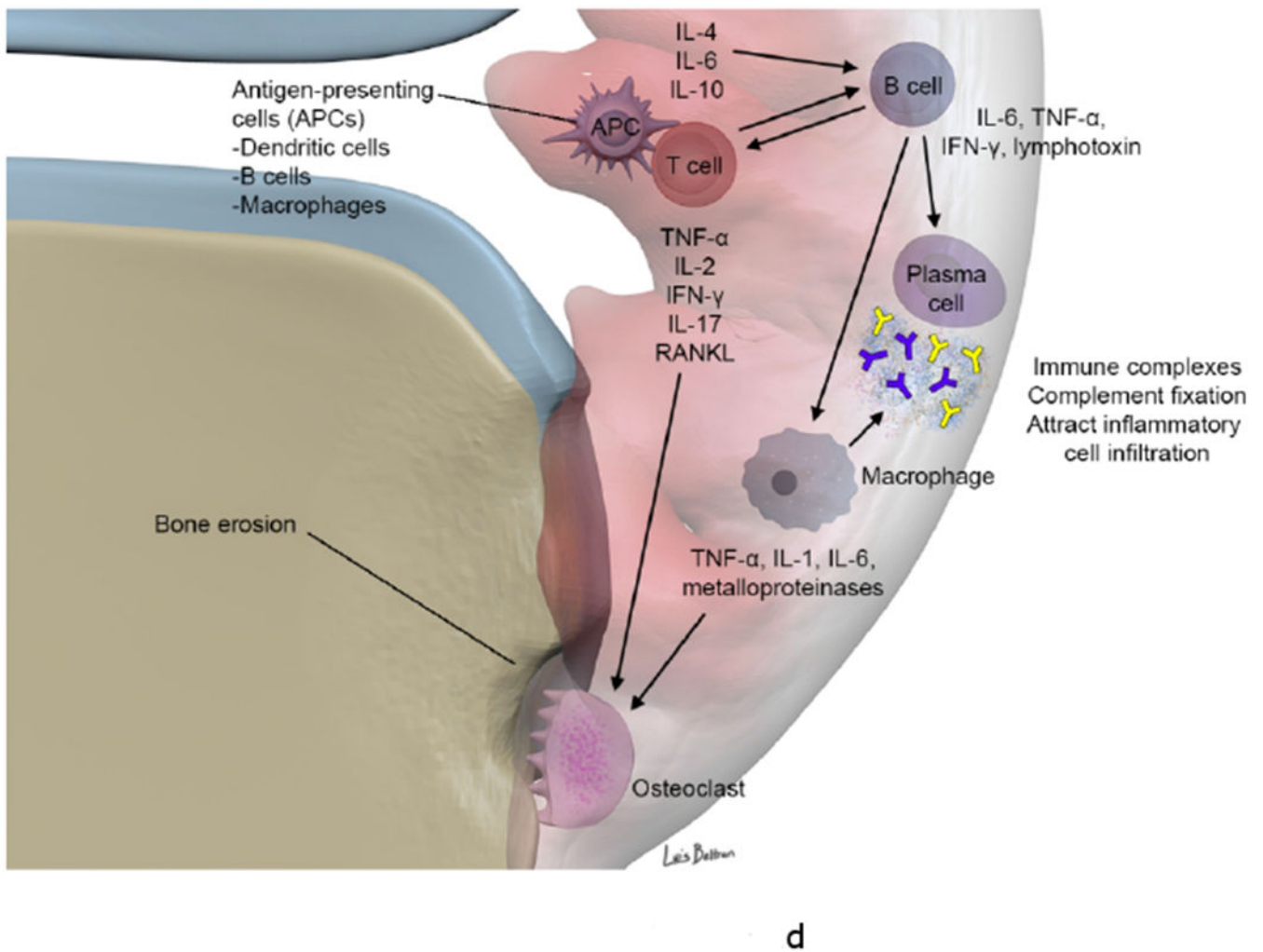
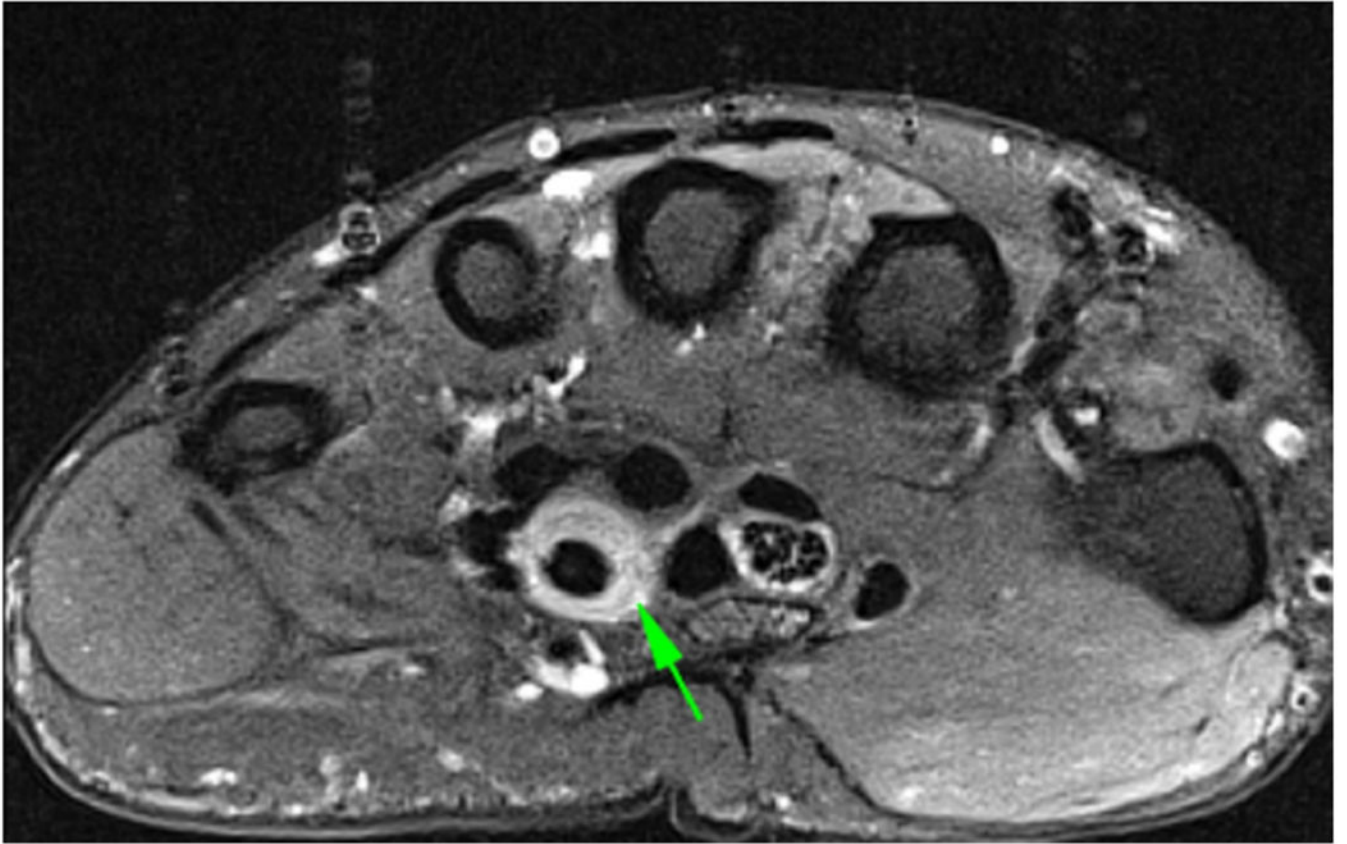


Figure 1.
(a-b). Synovial involvement in OA pathophysiology. Degraded cartilaginous products within synovial fluid are phagocytosed by activated synovial cells within the inflamed synovium which in turn produce proinflammatory and catabolic mediators. Proteolytic enzymes promote cartilage breakdown creating a positive feedback loop. Inflammatory cytokines promoting enzymatic mediators of cartilage catabolism include MMPs and ADAMTS. The inflamed synovium also contributes to osteophyte formation via BMPs. Activated infiltrating macrophages, synovial B cells and T cells amplify this inflammatory response however the synovium and cartilage may also produce counteracting anti-inflammatory products such as IL-4, IL-13, IL1Ra and TIMPS.
(c-d). Synovial involvement in RA pathophysiology. The synovium is infiltrated with mature antigen presenting cells (APCs) (including dendritic cells, macrophages and B cells) and activated T lymphocytes, which interact to initiate and amplify T-cell-dependent immune responses, promoting chronic synovial inflammation. Activated T cells induce secretion of pro-inflammatory cytokines (in particular TNF α) from macrophages and synovial cells in a contact-dependent manner. Macrophages also function as osteoclast precursors, as well as providing specific molecular signals driving osteoclast formation. Numerous osteoclasts are

found within the inflamed synovium adjacent to bone, creating resorption pits and causing local bone destruction through specific enzymes and a proton pump that enable them to degrade bone matrix and solubilize calcium. RANKL binds to receptors of pre-osteoclasts and mature osteoclasts and stimulates their activation and differentiation (together with TNF, IL-17 and IL-1). B cells contribute to immune complex formation and complement activation, act as APCs and contribute to T cell activation through expression of costimulatory molecules. B cells both respond to and produce the chemokines and cytokines that promote leukocyte infiltration into the joints, angiogenesis, and synovial hyperplasia. ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs, BMP bone morphogenetic protein, CXCL13 CXC-chemokine ligand 13, EGF endothelial growth factor, IFN- γ interferon γ , IL interleukin, IL-1Ra IL-1 receptor antagonist, LTB₄, leukotriene B₄, MMP matrix metalloproteinase, NO nitric oxide, RANKL receptor activator of nuclear factor κ B ligand, TIMP tissue inhibitor of metalloproteinase, TNF tumor necrosis factor, VCAM, vascular cell adhesion molecule 1, VEGF vascular endothelial growth factor.





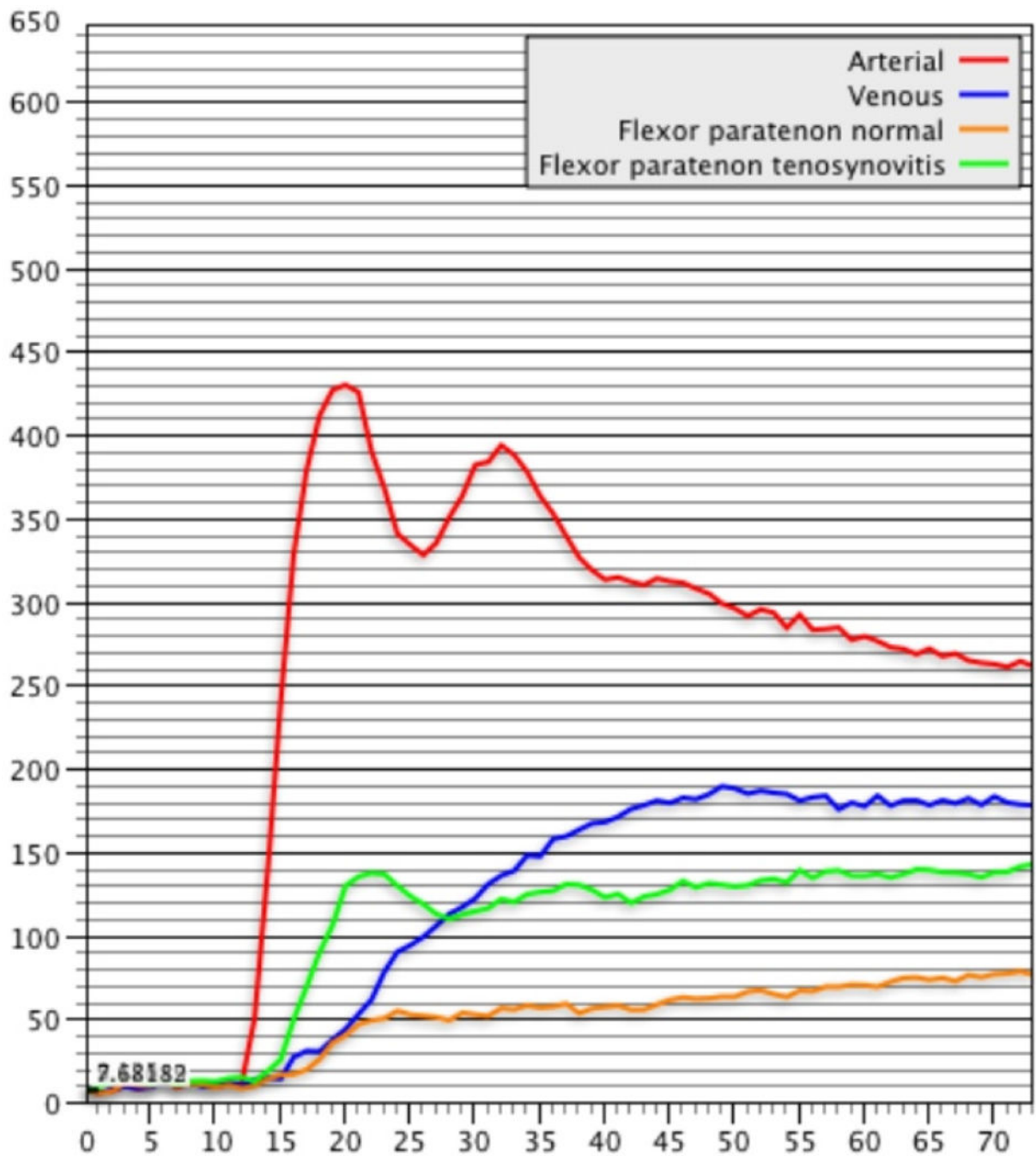
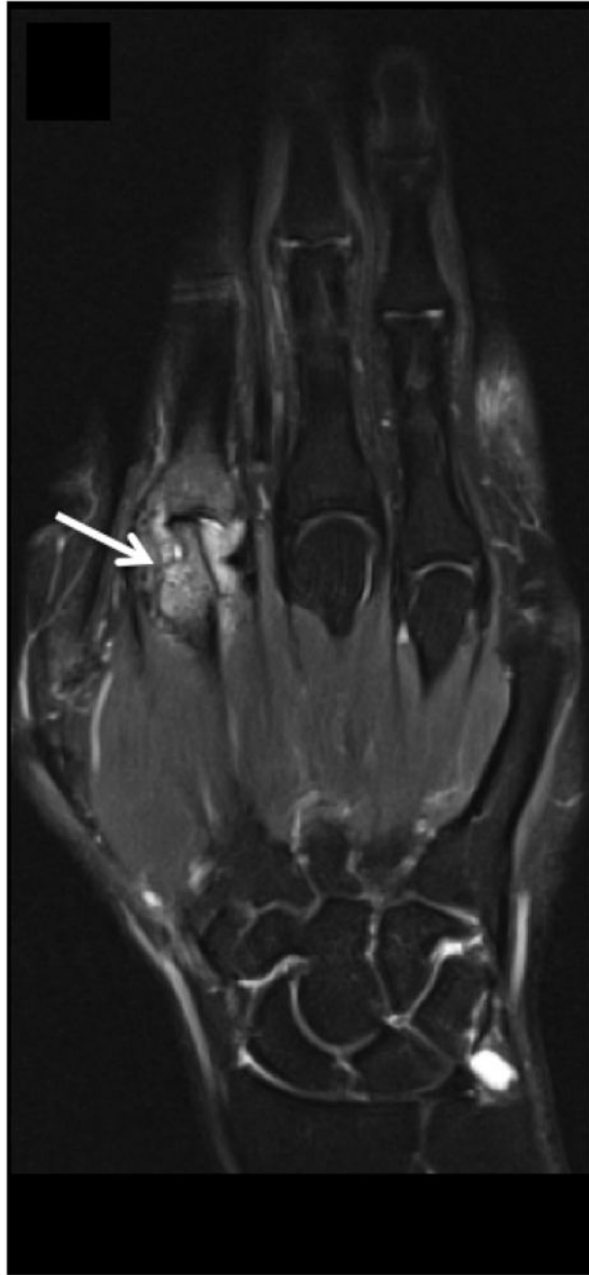


Figure 2.

DCE-MRI of a patient with known Rheumatoid Arthritis and wrist pain. Axial (a) and Coronal (b) fat-suppressed post-contrast images demonstrating flexor tenosynovitis (green arrows). A corresponding time intensity curve (c) (y-axis=signal intensity and x-axis=time) shows fast initial enhancement followed by a plateau phase, with sustained late enhancement.



a



b



c



d



e



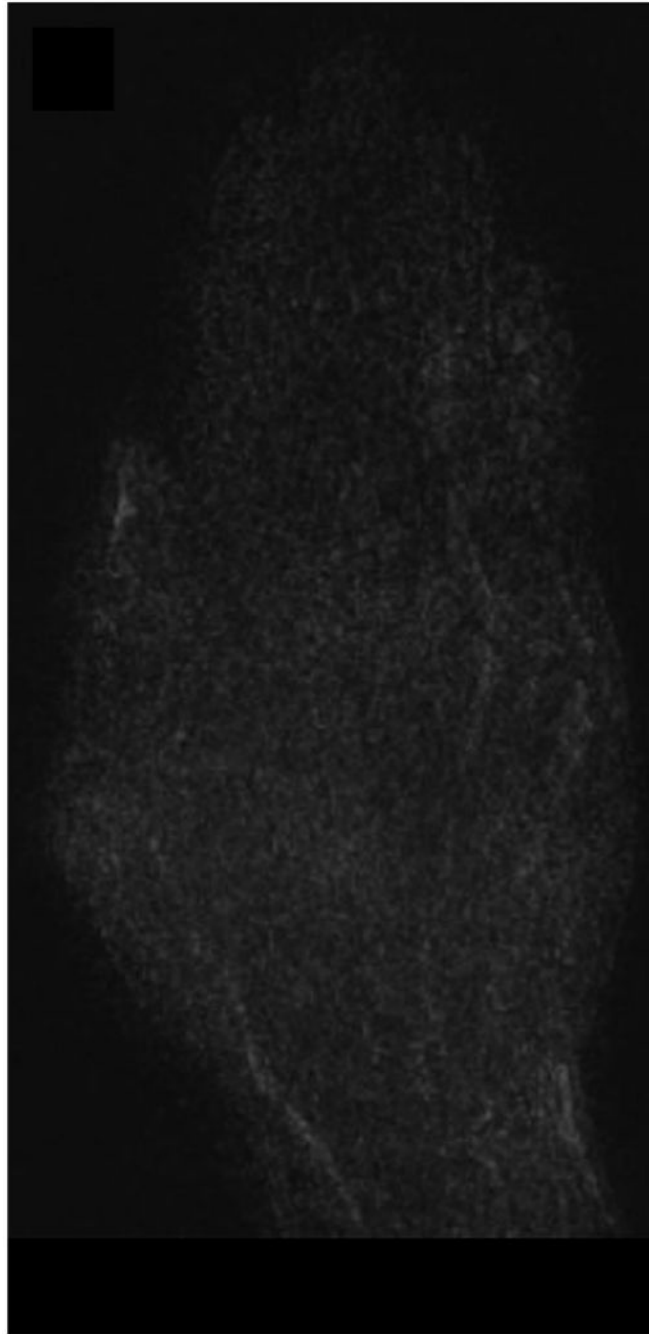


Figure 3. MRI of the right hand in a 29 year old male with Rheumatoid Arthritis recently diagnosed at baseline showing abnormal signal and erosion in the symptomatic 2nd mcp joint (arrows) on routine T1 and PD Fat saturated images (a, b). There is associated abnormal enhancement of the synovium indicated on the T1 post gadolinium enhanced images (c) and the dynamic contrast enhanced time resolved (TWIST) MIP sequence (d). 7 weeks after Anti-TNF treatment, MRI of the right hand showing abnormal signal and erosion in the symptomatic 2nd mcp joint (arrows) on routine T1 and PD Fat saturated

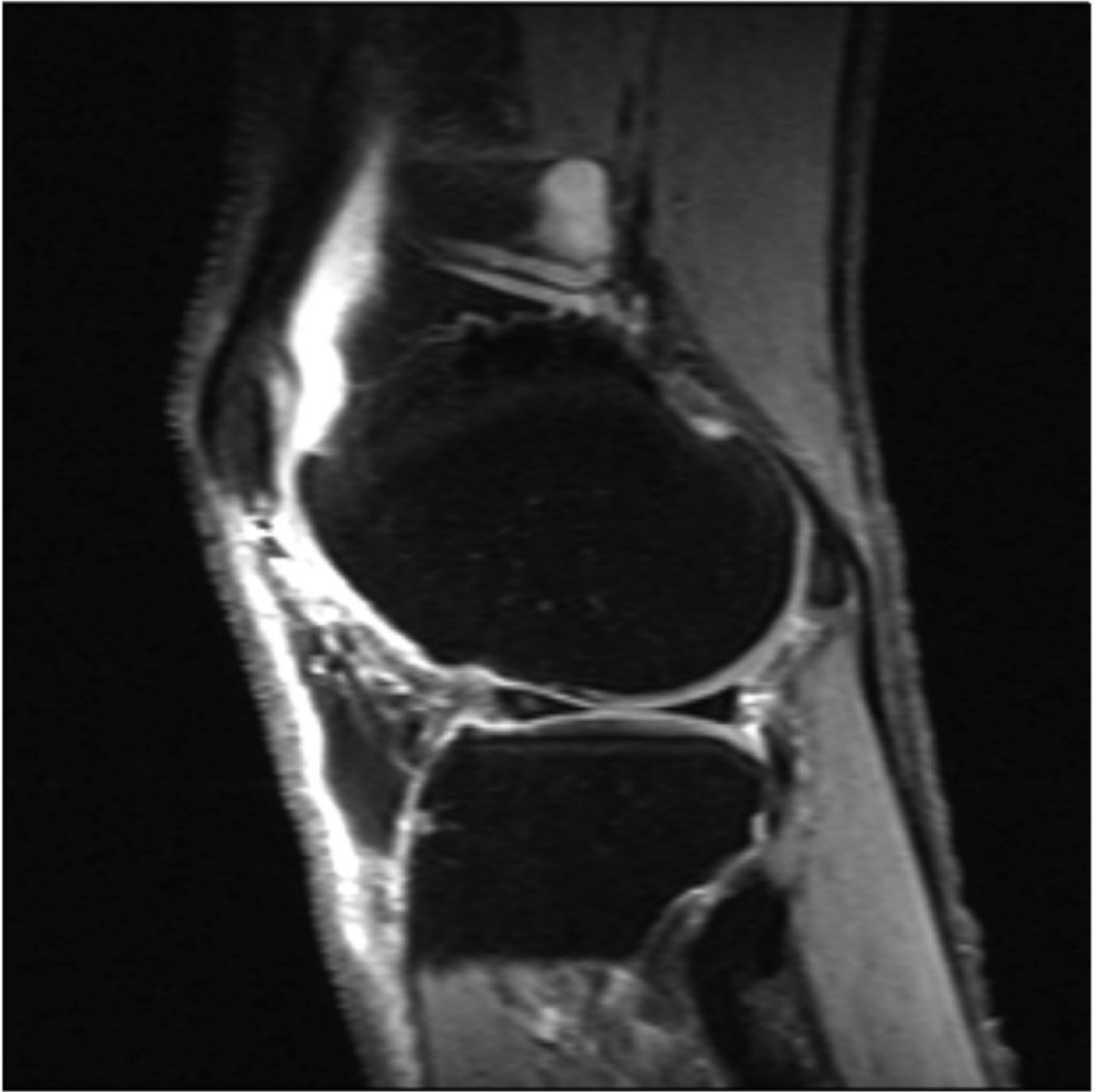
images (e, f), which does not appear to have changed significantly with treatment compared to the baseline MRI scan. However, the dynamic contrast enhanced time resolved (TWIST) MIP sequence (g) shows relative absence of enhancement in this region, which suggests decreased vascularity after treatment.

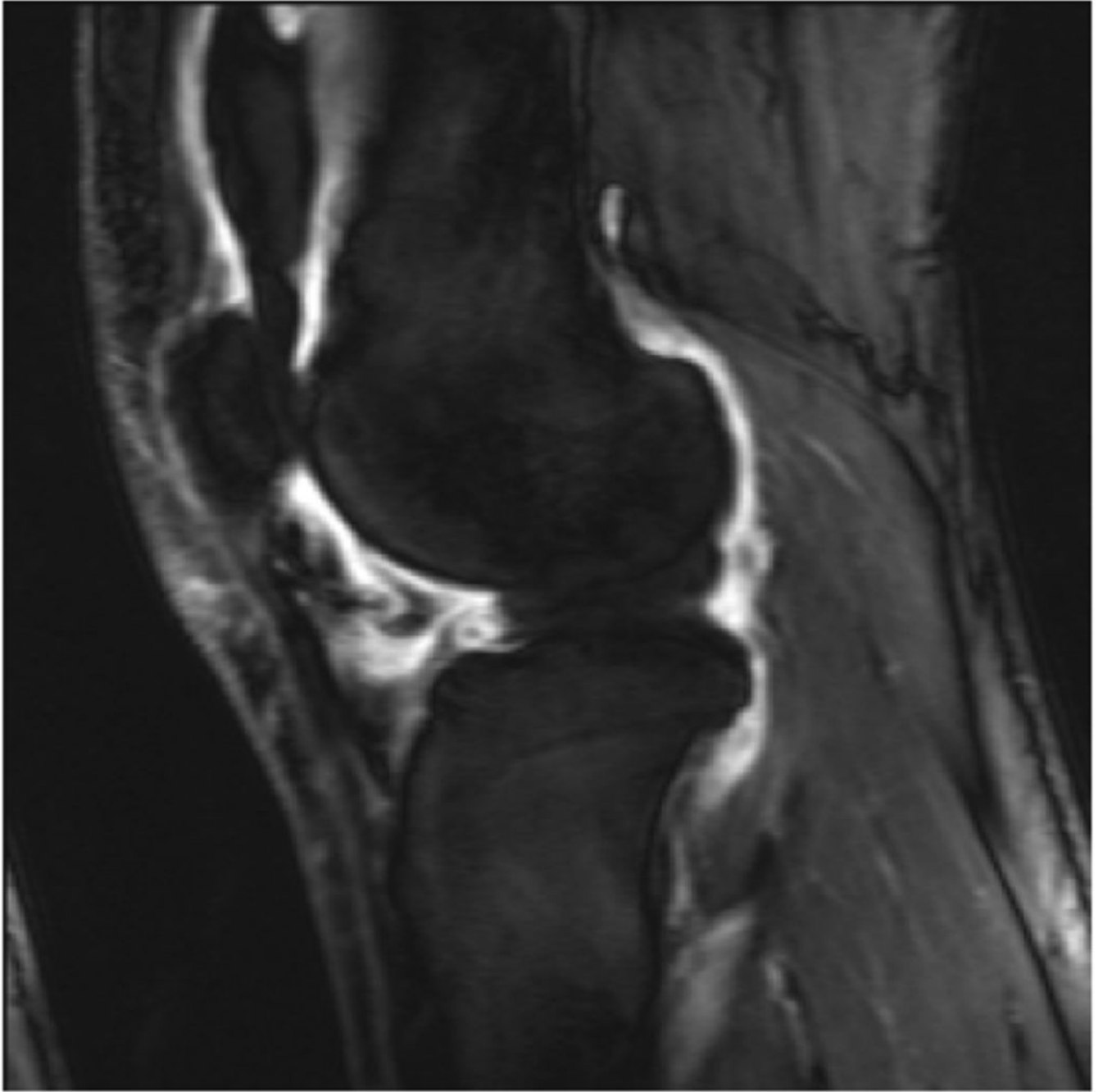
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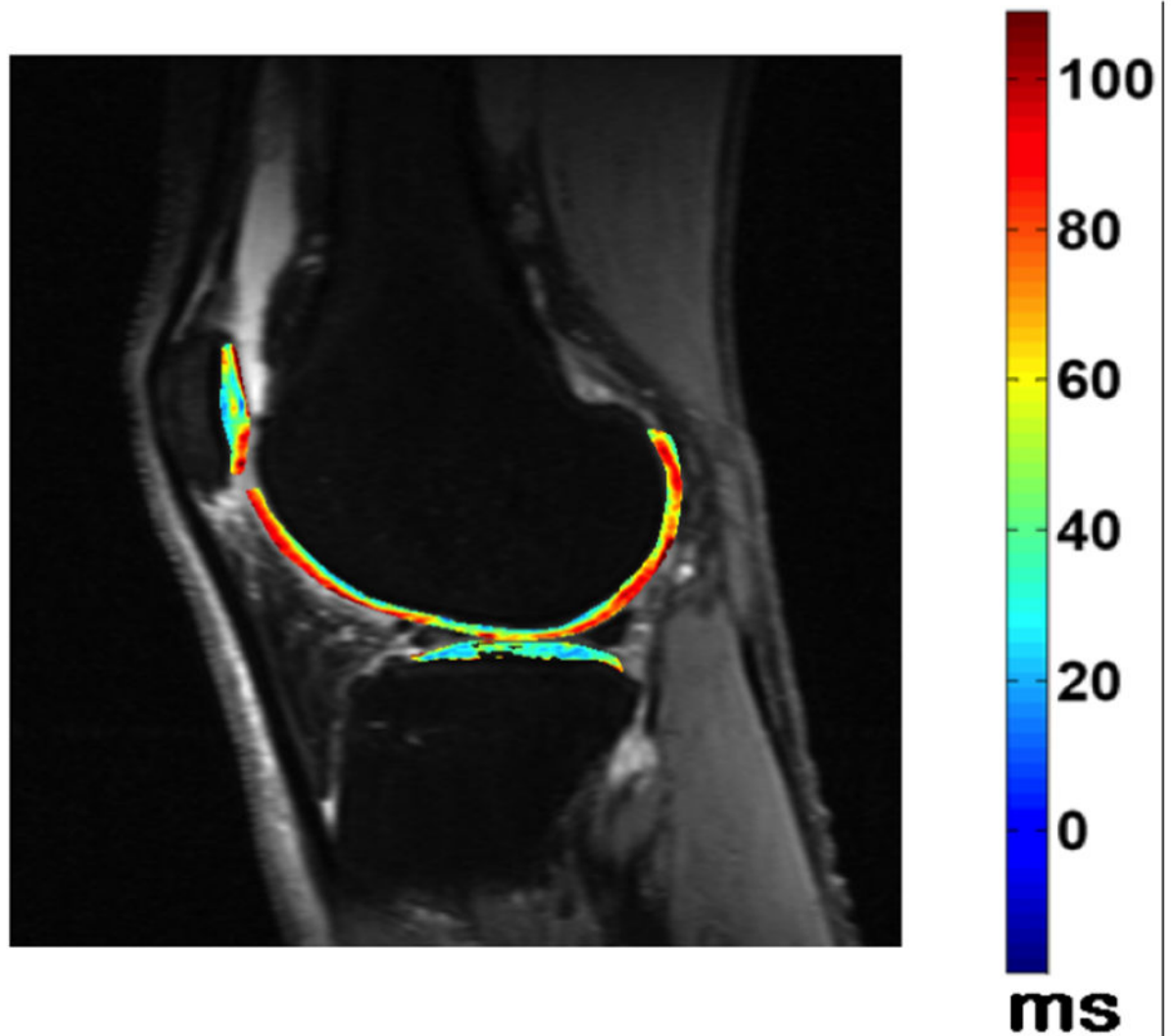
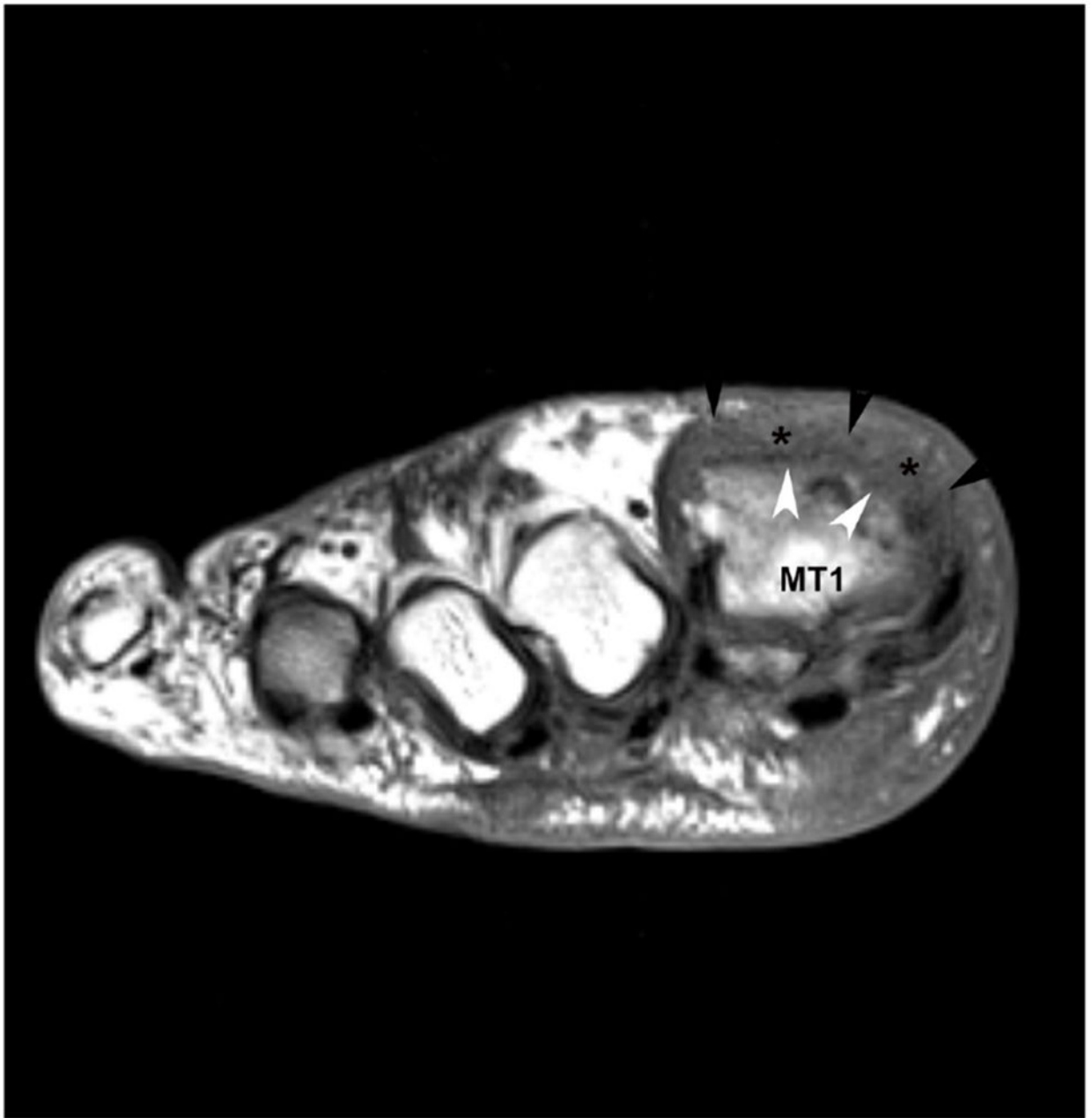
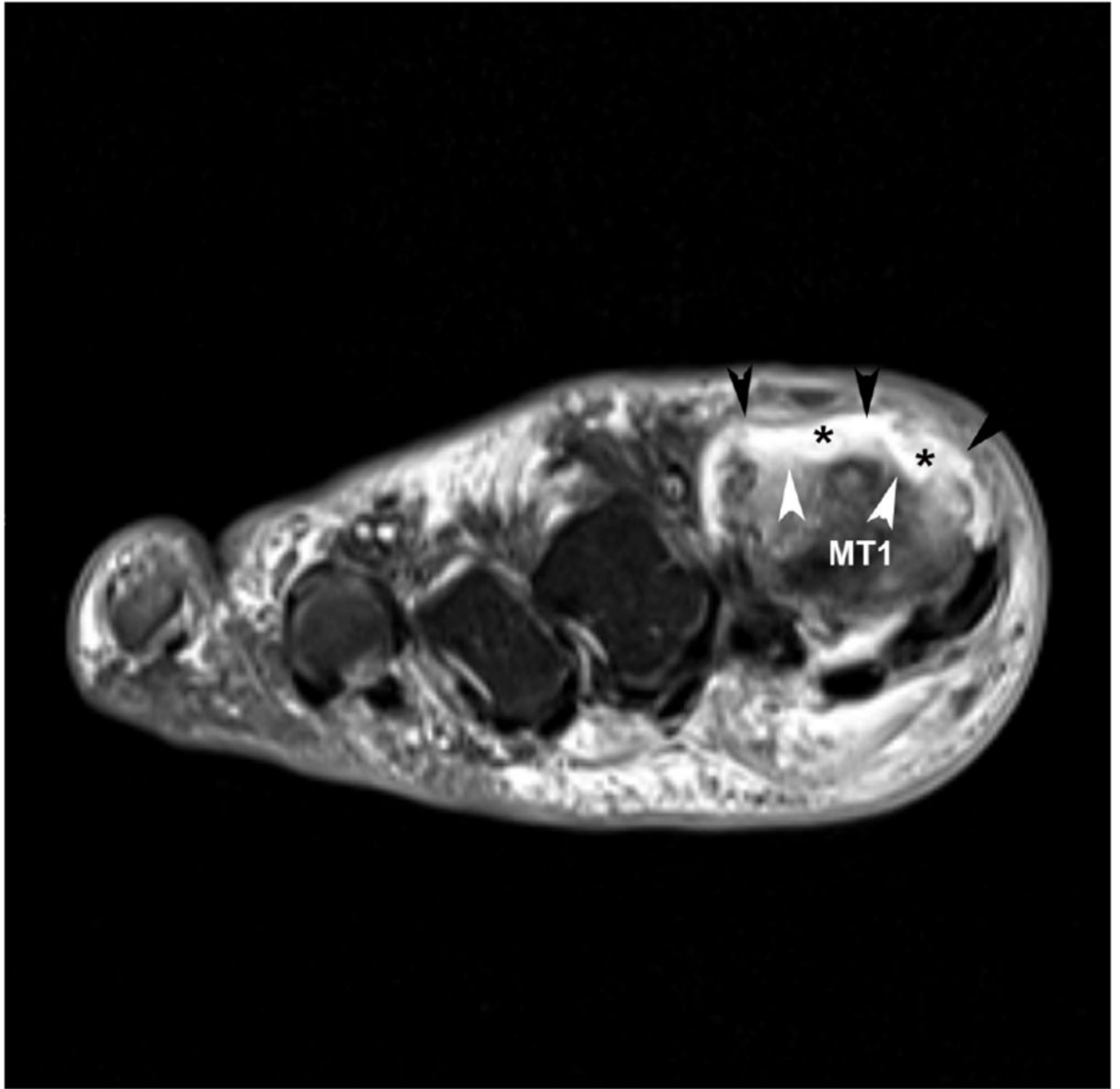


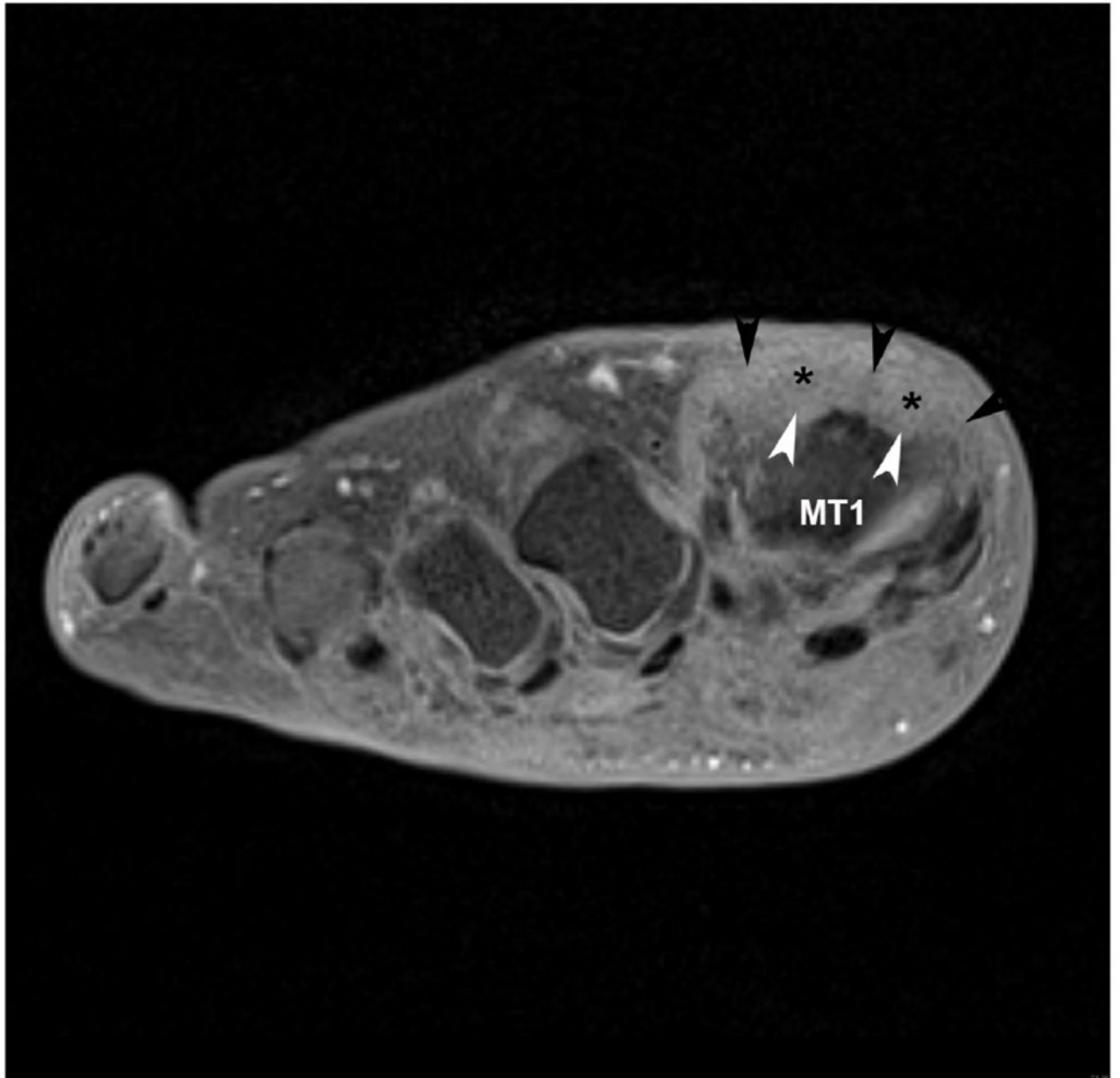
Figure 4 –. Fluid sensitive images in a patient with knee pain, demonstrating intraarticular increased signal intensity (a), which corresponds to increased synovial volume on contrast enhanced images (b). T1rho imaging with a color map of the cartilage in the lateral tibiofemoral compartment denoting areas of cartilage degradation.



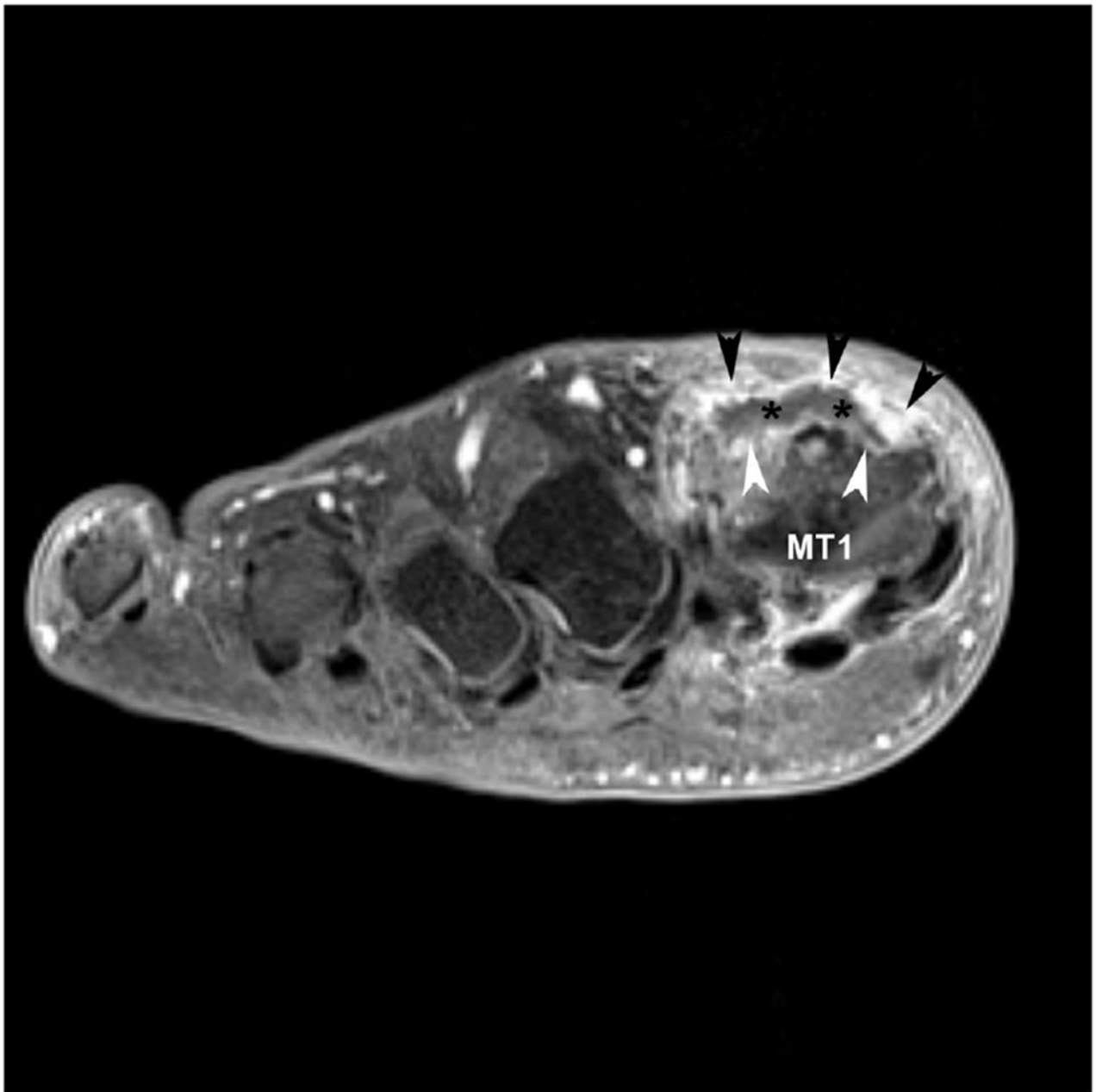
a



b



c



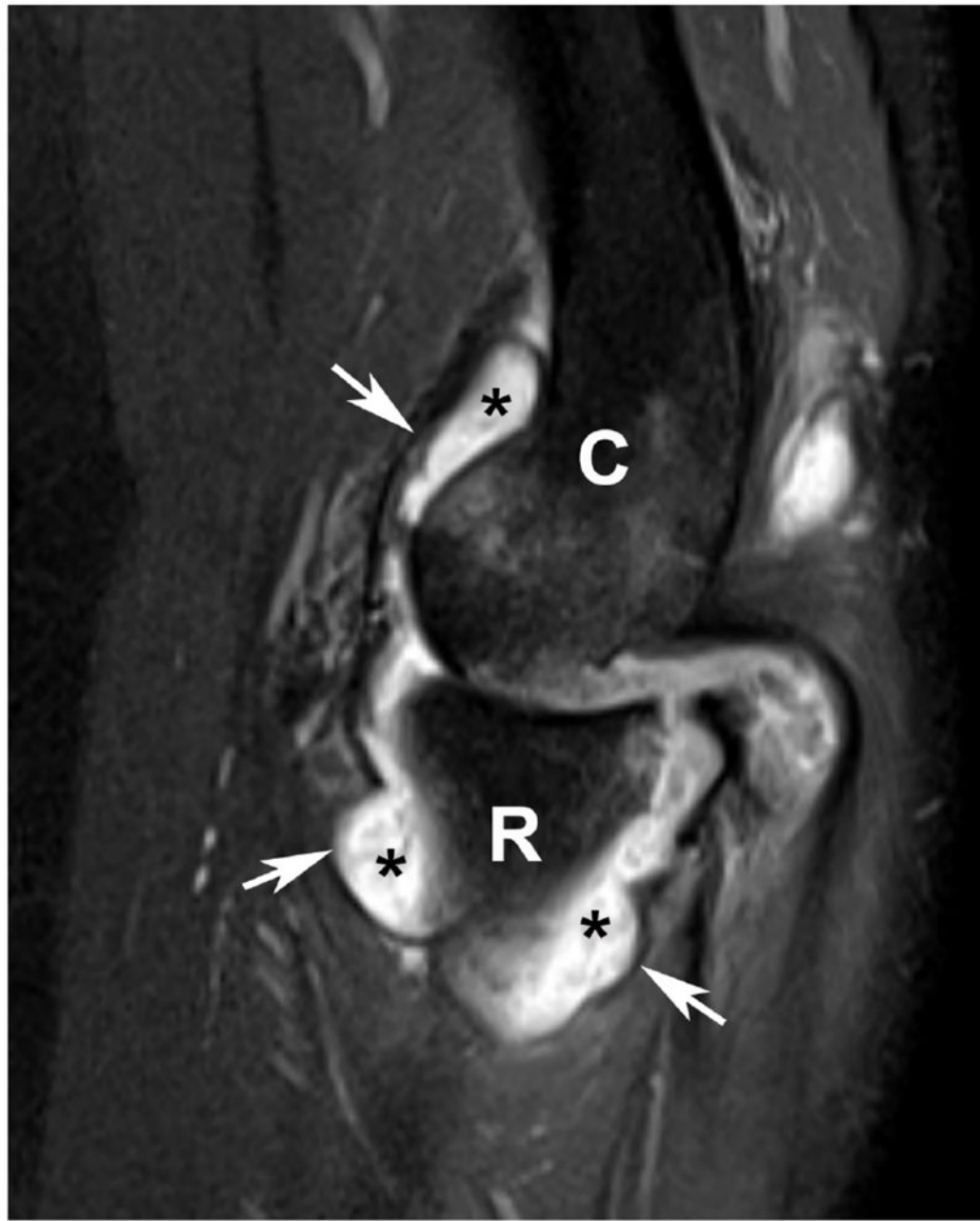
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Figure 5.

79 year old male with gout, confirmed by aspiration of monosodium urate (MSU) crystals. Short axis (a) T1 (TR 528 / TE 10) (b) T2 FS (TR 5610/TE 40), (c) T1 FS pre (TR 612/TE 10) and (d) post Gadovist contrast images (TR 670/TE 12) demonstrating an effusion (*) in association with synovitis of the first metatarsophalangeal joint distending the joint capsule (black arrowheads). There are osseous erosions (white arrowheads) of the first metatarsal head (MT1) with subjacent bone marrow edema.



a

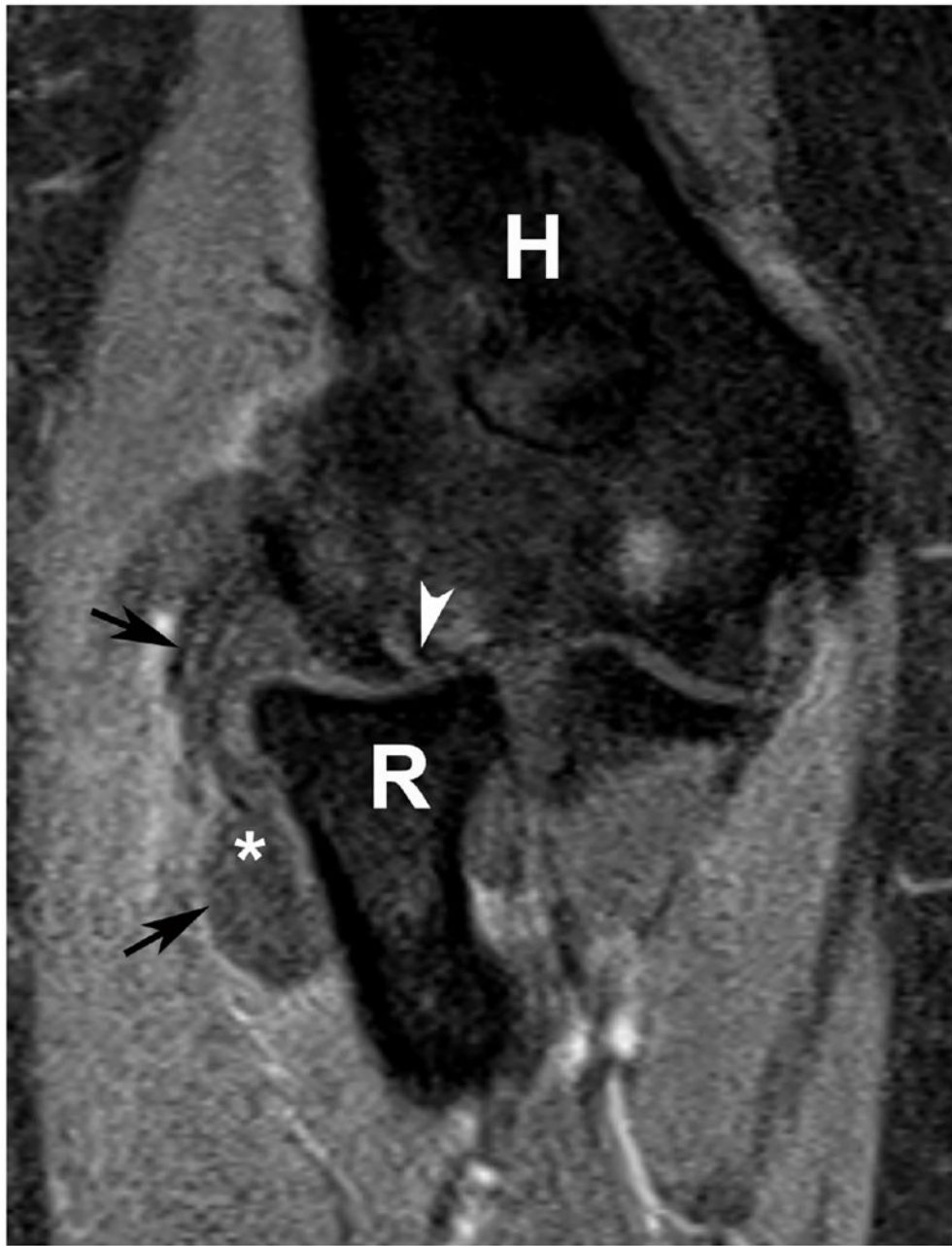


b

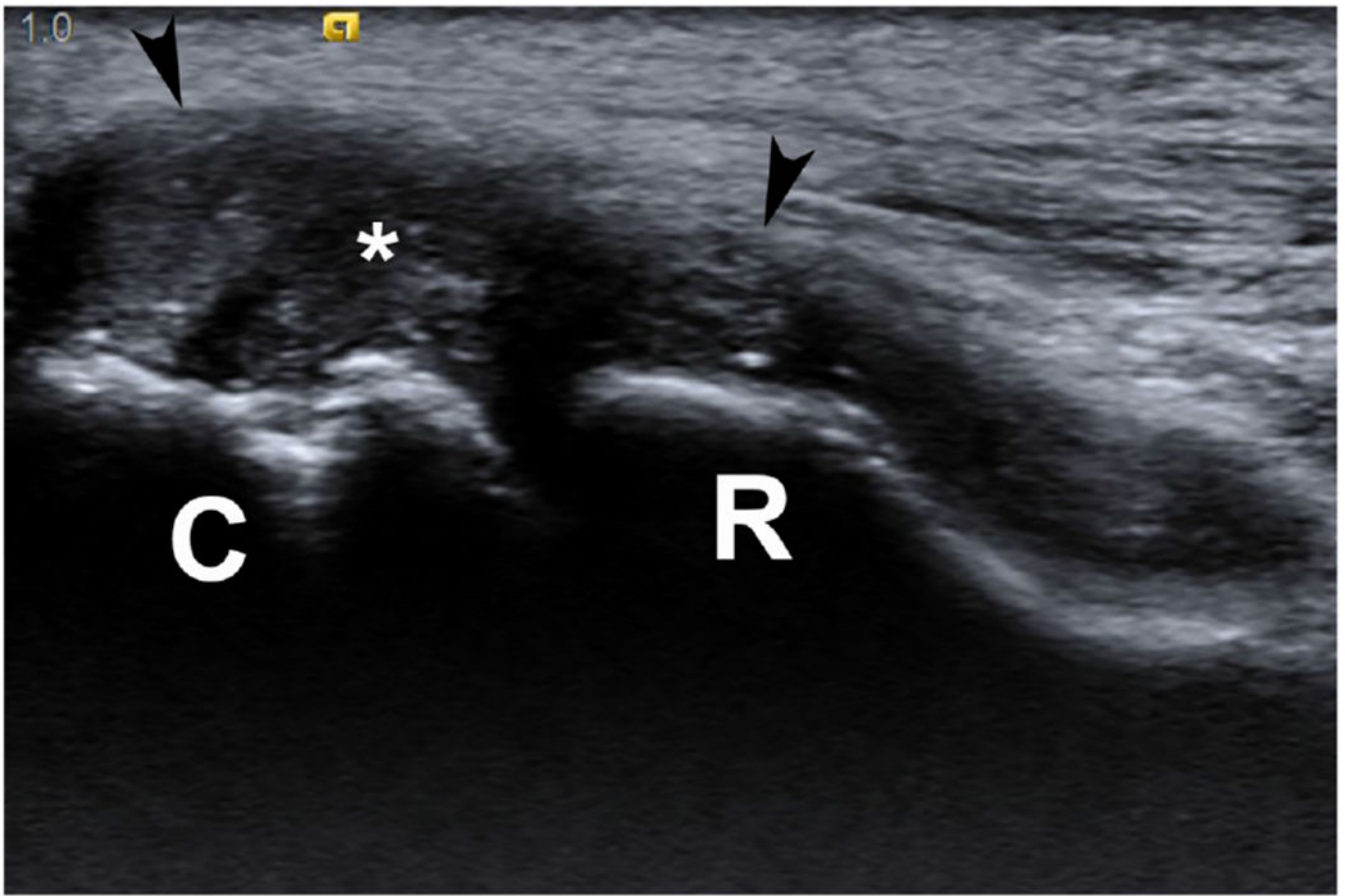




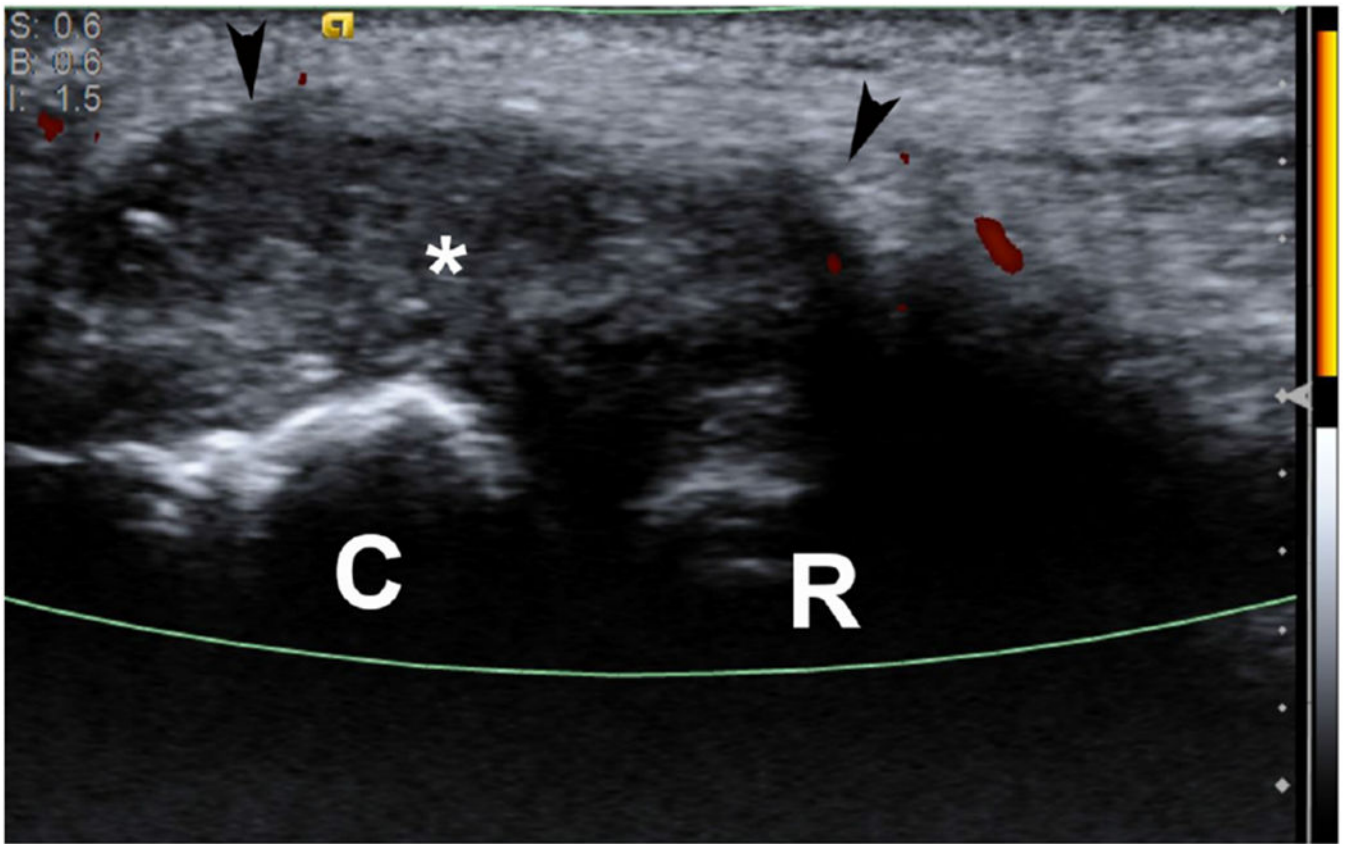
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e



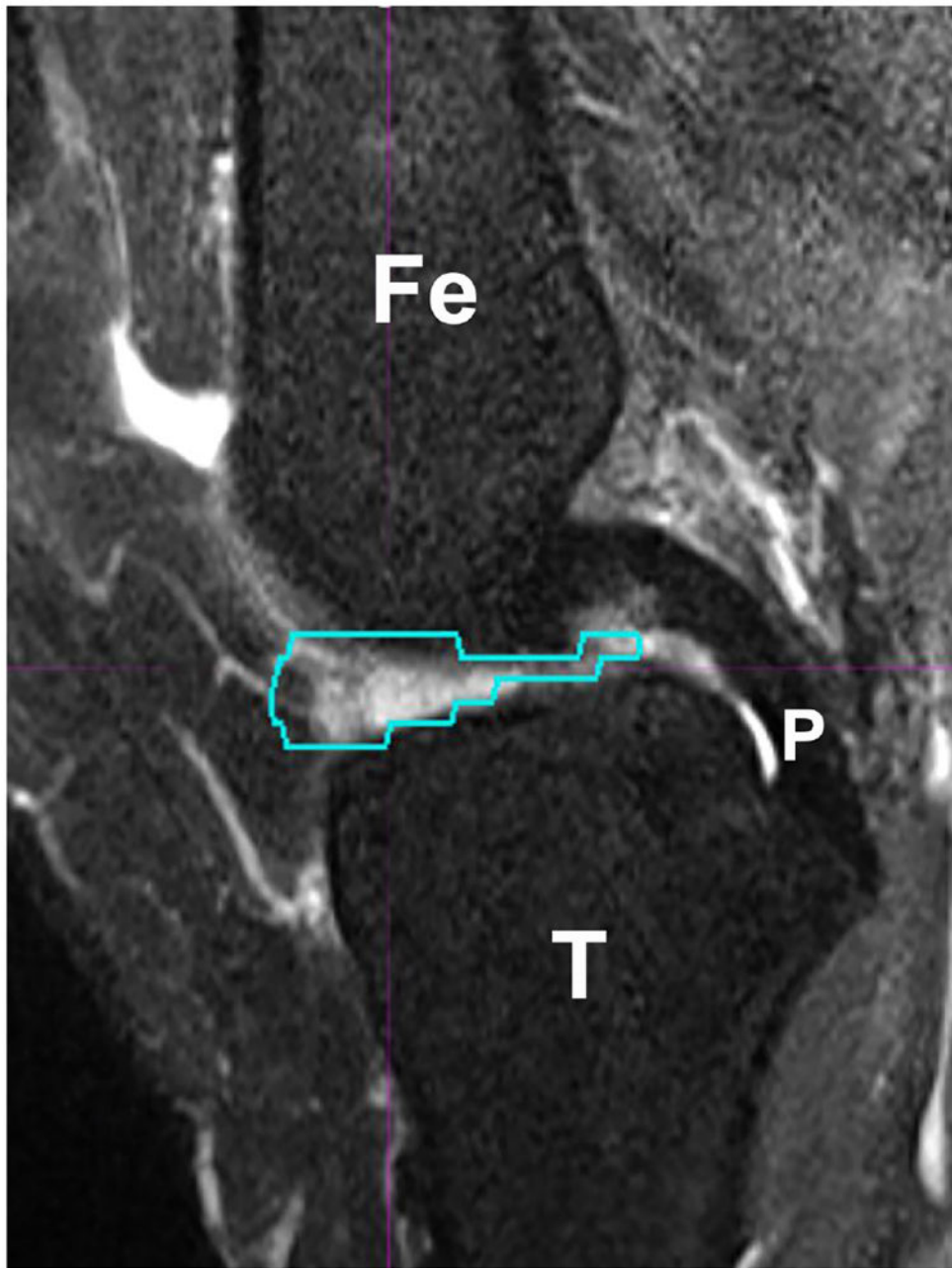
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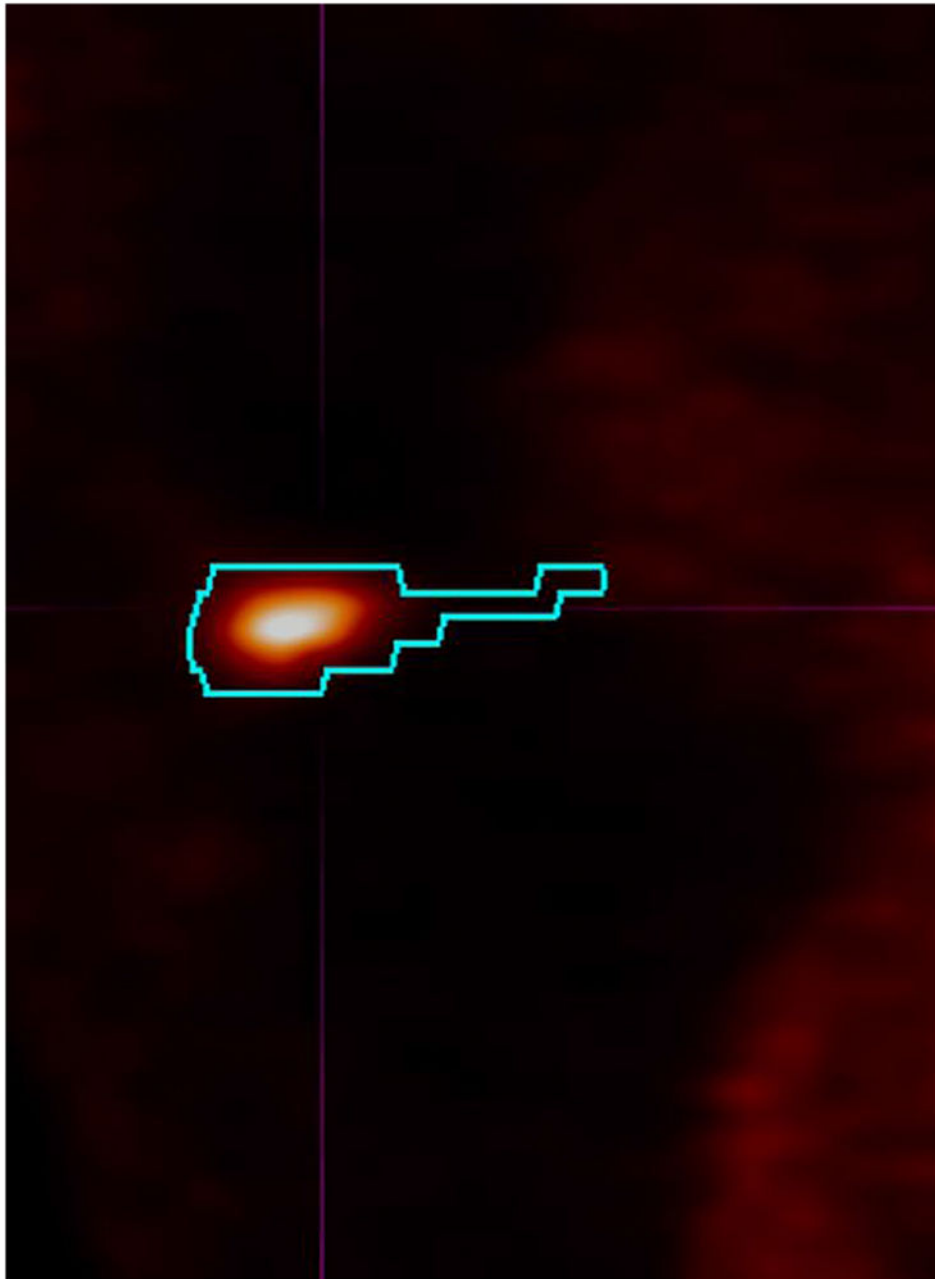
g

Figure 6.

37 year old female with RA. (a) Lateral elbow radiograph demonstrating elevation of the anterior (white arrow) and posterior (black arrow) fat pads, considered a plain radiographic sign of an effusion however cannot differentiate between synovitis and effusion. (b) Sagittal T2 FS (TR 4400 / TE 50), coronal (c) T2 FS (TR 4210 / TE 33), (d) T1 (TR 645 / TE 8.9) and (e) T1 FS post contrast (TE 846 / TE 8.9) images demonstrating high T2 signal non-enhancing synovitis and pannus formation (*) diffusely expanding the joint capsule (black arrows). A small osseous erosion is seen involving the capitellum (white arrowheads) with subjacent bone marrow edema. Gray scale (f) and Power Doppler (g) ultrasound images in the same patient demonstrating non vascularized hypertrophied synovium (*) distending the joint capsule (black arrowheads) compatible with the absence of enhancement on MRI. C – Capitellum; R – Radial Head; H - Humerus.



a



b

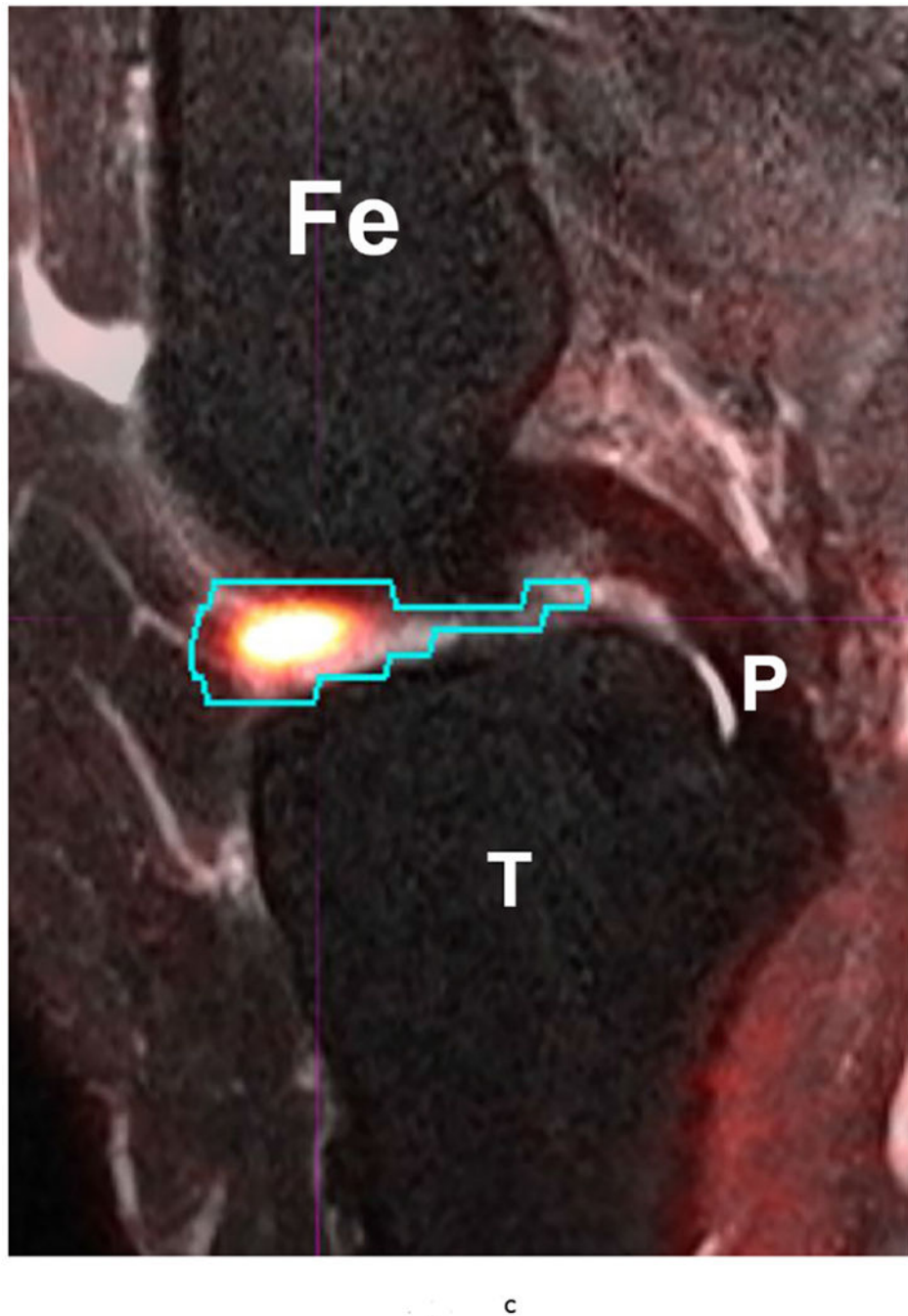


Figure 7. 53 year-old female with knee pain and early OA. Sagittal (a) T2 FS (TR 5160/TE 56) (b) 18 -FDG PET and (c) fused Hybrid MR PET images demonstrating 18 -F FDG avidity corresponding to synovitis in the anterior intercondylar notch. The region of interest is demarcated in turquoise and the SUVMax measured as 10.97. Fe – Femur; T – Tibia; P – Posterior Cruciate Ligament.

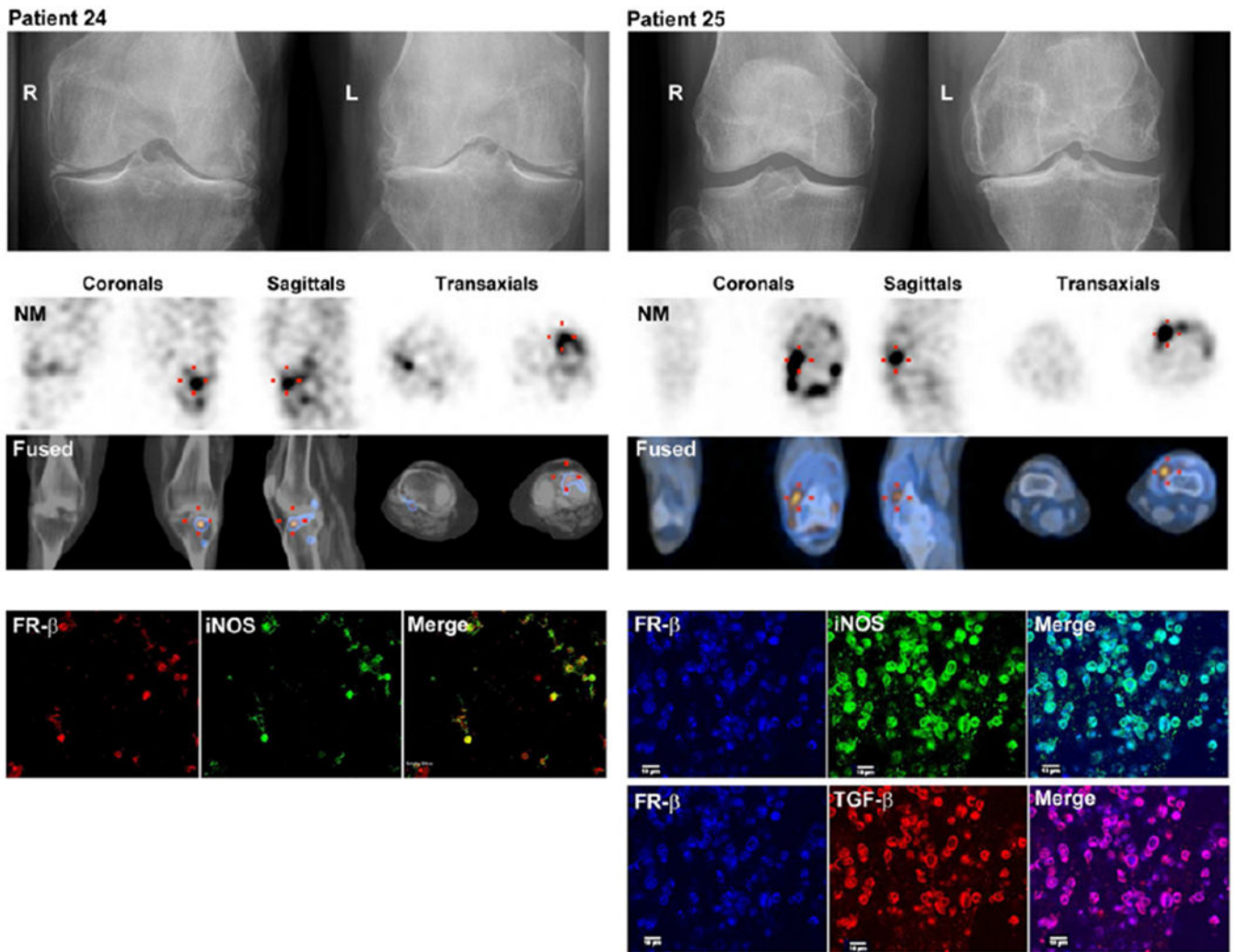


Figure 8.

Representative images (top row) of Etarfolatide uptake in the: A) joint ‘capsule’ (showing capsular and/or underlying synovial uptake, indicated in coronal view by arrowhead); B) ‘synovium’ (showing uptake by proliferative synovium in the posterior synovial recess, indicated in coronal and sagittal views by arrow); C) ‘synovium’ and joint ‘capsule’ (indicated in sagittal view by arrow and arrowhead, respectively); and D) bone (indicated in coronal view by asterisk). Heat map graphic (bottom) representing the uptake intensity for each knee as quantified for three regions: joint ‘capsule’, ‘synovium’ and subchondral bone; the maximum score for each joint region was 6, 6 and 5, respectively. Reprinted from Kraus et al *Osteoarthritis Cartilage* 2016; 24 (9): 1613-1621, with permission.