REVIEWS

Quantifying synovial inflammation by imaging techniques

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Abstract

The past few decades have witnessed dramatic changes and advances in diagnostic imaging. In the field of arthritis, these changes have contributed to enhance the diagnostic accuracy and to conduct serial monitoring of synovial inflammation without synovial biopsy. Advanced imaging techniques employ target-specific probes to non-invasively assess molecular, cellular, and physiological abnormalities associated with the underlying pathology. Dynamic and diffusion magnetic resonance imaging (MRI) are being developed to evaluate the discrete aspects of specific inflammatory and destructive pathways of inflammatory arthritis. These newer imaging modalities provide an earlier and more reliable assessment of clinical outcome, disease activity, severity, location, and therapeutic response. These techniques will be incorporated soon in routine clinical practice, and their adoption may enable clinicians to measure the treatment response and tailor the therapeutic interventions accordingly. In this review, we have attempted to summarize the emerging non-invasive imaging techniques and their application in quantifying synovial inflammation.

Introduction

Inflammatory arthritis, characterized by synovial hyperplasia, infiltration of inflammatory cells, secretion of proinflammatory cytokines, and activation of matrix proteinases, causes damage to joint cartilages and bones. In acute conditions, inflammation is intense and the symptoms will appear early during the disease course. However, for chronic inflammatory conditions, the inflammation is persistent, and of low grade intensity. In inflammatory arthritic conditions like rheumatoid arthritis, psoriatic arthritis, and osteoarthritis; monitoring joint inflammation is difficult due to the associated limitations of serological and surrogate markers that are currently used to evaluate response to therapy. Moreover, current disease activity scores are a mixed bag of subjective and objective parameters and they do not correlate with actual synovial inflammation. Patients, classified as having remission by clinical or biochemical criteria, continued to demonstrate inflammation in synovium during imaging.[1] These limitations underscore the need for developing imaging techniques that are sensitive enough to diagnose even mild asymptomatic synovial inflammation. Various imaging modalities like MRI, ultrasonography, positron emission tomography

(PET), and bone scintigraphy have been used to assess the inflammation in the joints. In the present review, we will be focusing on some of the recent advances in the field of imaging with special focus on joint inflammation.

Ultrasonography

In recent years, ultrasound (US) has become a valuable tool and is considered as a bedside procedure for diagnosing and monitoring inflammatory arthritis.[2] The technique assists in identifying joint effusion, synovial proliferation, tenosynovitis, and subclinical synovitis with high precision. Outcome measures in Rheumatology Clinical trials (OMERACT) and European League against Rheumatism (EULAR) have proposed US definitions for common pathological lesions including joint effusion, synovial proliferation, tenosynovitis, and joint erosion using grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS).[3] GSUS is useful for differentiating fluid (effusion) and other morphological details (tendon, cartilage, bone etc.) depending on their echo texture; whereas, PDUS is very sensitive in detecting vascularity (active inflammation). Normal synovial tissue generally does not produce any Doppler signal. But an increase in power Doppler signal has been observed in

joint inflammation due to synovial hyperemia. In GSUS, synovitis is subjectively graded from 0 to 3 (0 = normal; 1 = mild; 2 = moderate; 3 = marked) and the PD signal on a semi-quantitative scale from 0 to 3 (0 = absence or minimal flow; 1 = mild: single vessel signal; 2 = moderate: confluent vessels; 3 = marked: vessel signals in >50% of the joint area) in images with maximal enhancement.[4, 5]

The USG measurement of inflammation is highly useful in identifying subclinical synovitis in patients with clinical remission and also for predicting relapse. PD signal, which has been found to correlate with clinical remission, predicts relapse better than GSUS.[6, 7] Additionally, PD signals correlate significantly with radiological progression.[7] A study by Scirè et al. have concluded that persistent PD signal predicted short-term clinical relapse of early RA patients in clinical remission.[8] Hence, presently followed criteria for clinical remission may not be ideal for deciding tapering of disease modifying therapy. The adoption of newer criteria based on US findings (mainly PD signal) may help in defining true remission in inflammatory arthritis. However, more studies are needed to validate the exact cut-off to be followed in defining clinical remission, thereby to avoid overzealous treatment.

Spectral and color Doppler are useful in estimating degree of synovial inflammation by calculating more objective measures like color fraction (CF) and resistive index (RI). CF is defined as the number of color pixel divided by the total number of pixels in region of interest (ROI). Number of color pixel corresponds to area of increase blood flow; whereas, total number of pixels in ROI is an estimate of the synovial membrane volume. In normal resting musculoskeletal tissues, RI is 1.00 due to the absence of diastolic flow. In case of increase tissue perfusion due to inflammation, RI becomes less than 1 indicating low peripheral resistance.[9] The exact cut-off level of RI to be used for diagnosing inflammation in synovitis is yet to be established.

Several studies have evaluated the effectiveness of color and power Doppler to quantify inflammation in inflammatory arthritis. A preliminary data analysis of PDUS, done before and after treatment with glucocorticoids, has suggested that the technique may aid in assessing serial changes in synovial inflammation.[10] Szkudlarek et al. have reported the technique as an objective measure of inflammation by calculating change in CF before and after treatment with glucocorticoids and the measure has been found to be comparable to that of the changes in histology and MRI.[11]

Another study by Terslev et al. demonstrated that the decrease in CF, following treatment with intraarticular steroid, paralleled with an increase in RI and both the measures correlated with changes in ESR, VAS, and tender joint count.[12] Intra- and inter-observer correlation coefficients estimated for CF were 0.82–0.97 and 0.81 respectively.[9] However, validation of various scoring systems is required before incorporating them in day-to-day clinical practice.

Evidence indicates that the findings of contrast-enhanced ultrasonography (CEUS) using encapsulated microbubble is comparable to that of MRI and it is sensitive enough to identify hypervascularity in RA synovitis.[13] After few minutes of injection, the capsule dissolves in blood and is eliminated by expiration. Peak enhancement is reached after 30 seconds and vascularity of the synovium can be calculated by duration and intensity of enhancement. Other recently developed US techniques include 3D/4D ultrasonography and fusion imaging.

The major advantages of US over other imaging modalities are greater sensitivity, cost effectiveness, easiness to perform in OPD and can be repeated for serial monitoring of inflammation, as required. Further, multiple joints can be studied in a short time. However, its major disadvantage is that it is less sensitive and very much operator dependent.

Computed tomography (CT) scanning

CT is regarded as the gold standard for imaging erosions and there are a few literature studies on its use in assessing synovitis.[14-16] Multidetector helical CT produces high-quality images that can be stored and used for serial assessment. Studies indicate that CT scan of wrist of RA patients outperformed MRI in erosion detection and similar findings have been reported for metacarpophalangeal (MCP) joints.[16,17] CT has also been used to monitor progression of erosions in patients on anti-tumor necrosis factor therapy.[18] Compared to other diagnostic imaging procedures, CT scans result in relatively high radiation exposure. This exposure may be associated with a very small increase in cancer risk.[19]

A new CT technique, termed as 'Microfocal CT' (micro-CT), allows volumetric assessment of bone mineral density. In one of the studies, conducted in RA patients and healthy controls, small erosions were observed in both the groups.[20] However, lesions >1.9 mm in diameter were found to be highly specific for RA. RA erosions were mostly found along the radial aspect of the metacarpal heads. In

a study, tocilizumab was observed to repair erosions and has a favorable effect on local bone remodelling in RA.[21]

Another CT-based imaging technique that will assist in diagnosing periarticular osteopenia in early RA is CT osteoabsorptiometry.[22] Mineralization at the MCP joints was significantly reduced in all the groups of RA patients, including those with early disease, compared to controls (P <0.004). Volumetric bone mineral density (vBMD) using a peripheral quantitative CT (high-resolution-peripheral quantitative CT, HR-pQCT) system confirmed the involvement of the trabecular bone compartment in periarticular osteopenia.[23] Most of the aforementioned CT- based imaging techniques and further investigations are mandatory to confirm whether they are adoptable in real clinical scenarios.

MRI for assessing synovitis
Magnetic resonance imaging (MRI) is the most sensitive technique for evaluating joint inflammation. Conventional MRI T1-weighted spin-echo sequence carried out before and after intravenous contrast administration may assist in differentiating synovial inflammation from the joint effusion.[24] MRI-based measurement of synovial thickening and synovial fluid volumes are effective as markers for disease activity. The signal intensity, which reflects the severity of inflammation, is intermediate to low on T1-weighted images, but high on T2-weighted images owing to the high water content of synovial fluid and within the synovium.[25]

Fat-suppressed, T2-weighted images are effective in delineating synovial inflammation. Non-contrast heavily T2-weighted images may help in identifying synovial proliferation, which has lower signal intensity than effusion in the joint.[26] Contrast-enhanced T1-weighted sequences help distinguishing effusion from inflamed synovium.[27, 28] However, gadolinium-based contrast medium can rapidly diffuse into synovial fluid, causing equilibration of signal intensity between synovium and effusion within 5 min of administration. This in turn reflects the increased permeability of the synovial blood vessels during the inflammation.[28] MRI can also provide information about early synovitis. Bony erosions appear as focal areas within cortical bone where the normal signal intensity is lesser in T1- and higher in T2-weighted images. The administration of intravenous gadolinium (III)-diethyltriaminepentaacetic acid (Gd-DTPA) often enhances erosions, indicating the presence of inflamed synovium within the defect.

MRI studies of hand and wrist in RA have indicated that bony erosions develop much earlier than previously reported by plain radiography.[29-31] The exact time point for the onset of bone and cartilage erosions has not yet defined and it may vary among patients. McGonagle *et al.* have reported that 18 of 19 patients with symptoms for <1 yr demonstrated erosions of the dominant hand on MRI.[32] Similarly, Mcqueen *et al.* showed that 45% of the RA patients with symptoms for ≤6 had carpal MRI erosions at presentation, and it increased to 74% by 1 year. Bone marrow edema, which may precede erosions at the same site, is the characteristic MRI feature associated with inflammatory joint disease.[33] In another study comprising of 20 patients with recent onset knee effusion, peri-entheseal bone marrow edema was a prominent feature in six of ten spondyloarthropathy patients.[34] Although, MRI is a sensitive and advanced technique to assess inflammation, there might be chances of encountering false positive and false negative results even at very low levels of inflammation.

Dynamic contrast-enhanced MRI may delineate progression of synovitis
The transfer of contrast medium between intravascular and extravascular compartment of the synovium in dynamic contrast-enhanced MRI (DCEMRI) indicates increased and leaky angiogenesis in inflamed synovium. A T1-weighted MRI image is taken before and after infusion of a T1-shortening, diffusible contrast medium such as gadolinium. The post-contrast scan provides a time intensity curve that correlates with the concentration of contrast medium in the region of interest. The quantitation of synovial inflammation is based on pharmacokinetic model. The time intensity curve (TIC) aids in analyzing the exchange of contrast medium between the blood plasma and the extravascular extracellular space (EES).[35] The rate of transport between these two compartments and the concentration of contrast medium in the EES are dependent on the perfusion and permeability of the tissue specimen. DCEMRI is being increasingly validated for the detection of early synovitis. However, there are studies suggesting that antiTNFα therapy in patients with RA decreases the DCEMRI enhancement.[36] Study findings have also showed that quantitative DCEMRI findings correlated well with histological severity of inflammation in the knee joint and varied with intensity of inflammation following intraarticular steroid injection.[37-39] DCEMRI assists in measuring the vascular components, changes in blood flow, blood volume, and tissue permeability of the inflammation. The procedure also helps in monitoring early responses to DMARDs and biologics.

Quantifying synovial inflammation with diffusion tensor imaging

Diffusion tensor imaging (DTI) is a non-invasive, non-contrast-based MRI that provides microstructural information of the tissue through the measurement of diffusion of water molecules *in vivo*.This technique was initially used to study the structure of ordered biological tissues such as brain, myocardium and intervertebral disc.[40, 41, 42] Water molecules exhibit preferential diffusion in particular directions in tissues due to the presence of membranes and other structures to restrict the molecular diffusion (Fig 1). For example, water molecules diffuse more rapidly along the length of fibers compared to the perpendicular directions. This directional dependence is referred as anisotropic diffusion. This diffusion anisotropy aids in identifying tissue organization at microscopic level.[43] Unlike in pure liquids, where diffusion is isotropic and can be characterized by a single diffusion parameter, anisotropic diffusion (observed in tissues) is described by a 3×3 symmetric matrix. The two commonly used rotationally invariant scalar parameters that are derived from DTI are the mean diffusivity (MD) and fractional anisotropy (FA). MD, which is affected by the cellular size and integrity, is the average measure of the molecular motion independent of tissue directionality.[44-46] FA is a measure of the diffusion anisotropy. The minimum value of FA (zero) is achieved when diffusion is equally probable in all directions (isotropic diffusion) and has a maximum value of one for highly anisotropic structures such as thin fibers.

We have used DTI parameters to assess the severity of inflammation at the level of synovium in 18 patients with RA and 6 healthy controls. Significantly higher FA and lower mean diffusivity were observed in patients with RA compared to controls. Additionally, a strong positive correlation between FA and synovial fluid IL-1β and TNFα levels was observed (Fig 2, 3, 4).[47] Moreover, the observation of significant positive correlation between cylindrical isotropy (CP) and soluble intercellular adhesion molecule-1 (sICAM) suggested that the adhered inflammatory molecules on synovium simulate the planar model of diffusion tensor. These results support the hypothesis that restricted motion of water in the joints of patients with synovitis was a result of inflammatory cell aggregation. It has been suggested that this technique has the potential to replace synovial histology to assess the severity of inflammation and response to disease modifying drug therapy.[48]

Positron emission tomography (PET)

PET is a sensitive imaging technique based on positron-emitting radioisotopes. A positron loses energy during collisions with atoms and finally becomes annihilated after collision with an electron, resulting in the formation of two gamma rays. These two gamma rays travel away from the point of annihilation at 180 from each other. The PET detector registers these two photons (termed coincidence detection) along with their orientation. Circular PET detectors simultaneously register photons from multiple projections. Better anatomic definition of the tissue being scanned and spatial localisation of the PET signal are achieved through concomitant CT scanning. Most PET studies have been performed using the tracer [18F] flurodeoxyglucose ([18F] FDG), a radiolabelled glucose analogue that accumulates in metabolically active tissues found at inflammation sites.

Fig 1: Schematic diagram showing the conceptual view of diffusion tensor (DT) MR imaging technique
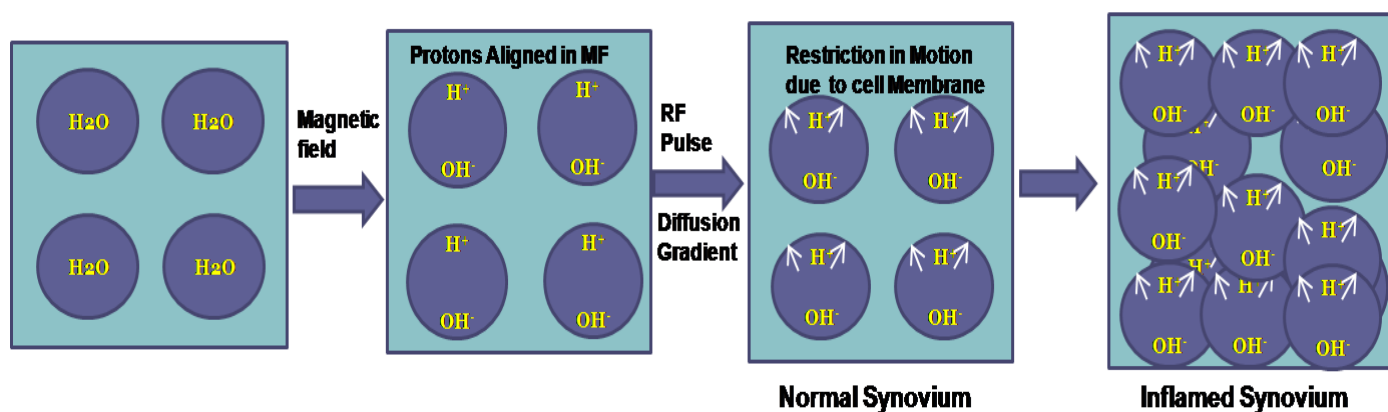
Water molecules arrange as H+ and OH- ions under the influence of strong magnetic field. These ions have equal tendency to move in all the directions, however due to obstruction created by the cell membranes this movement is restricted. This restriction is measured as fractional anisotropy (FA). FA is reciprocally related to mean diffusivity (MD).

Fig 2: Illustrated graph showing the comparison of healthy controls, patients at baseline, and those at follow-up for fractional anisotropy (FA) and mean diffusivity (MD)
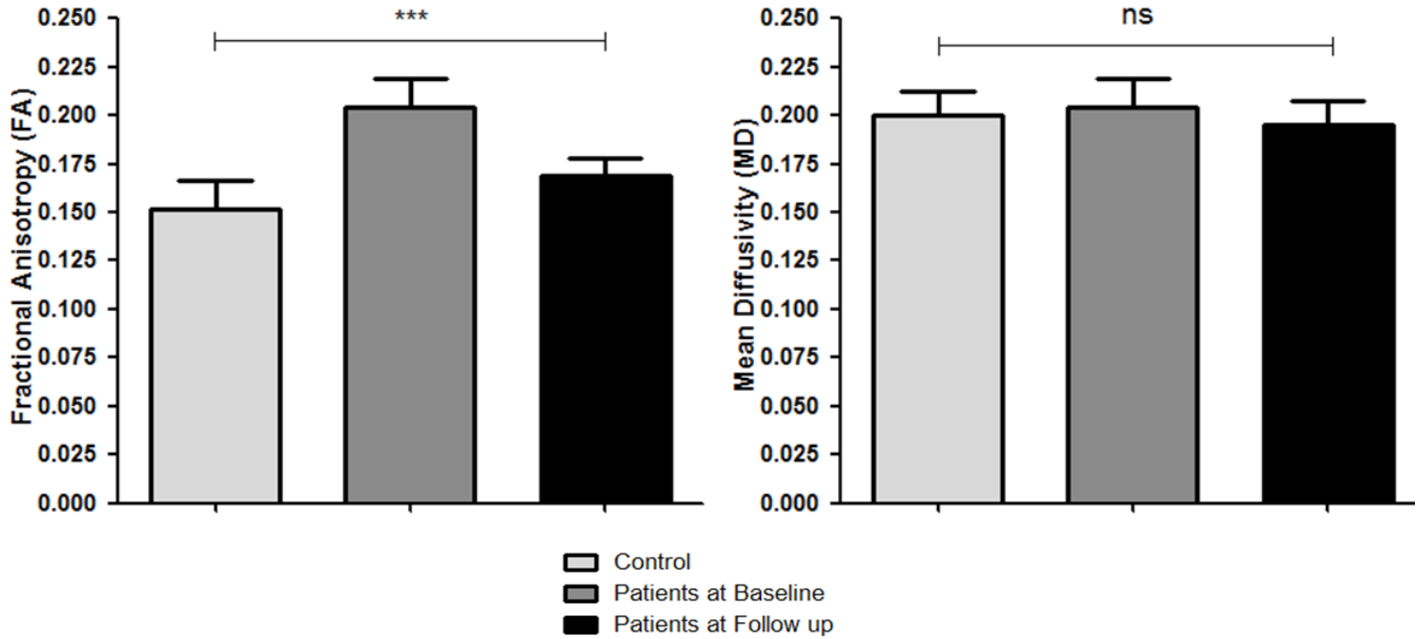

Control
Patients at Baseline
Patients at Follow up

Fig 3: Scatter plot showing the correlation between DTI-derived parameter FA and inflammatory cytokines TNF-α and IL-1β in synovial fluid of arthritis patients

TNF-α r=0.68 p =0.002
IL1−β r= 0.48 p =0.045
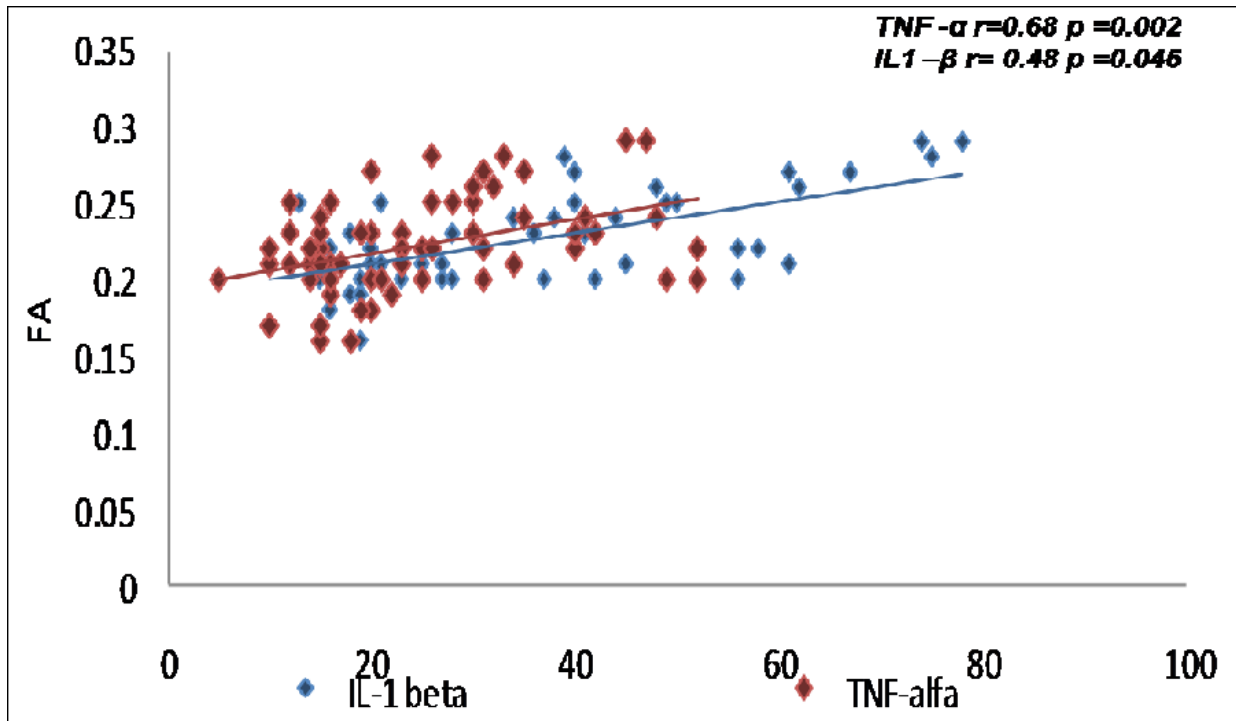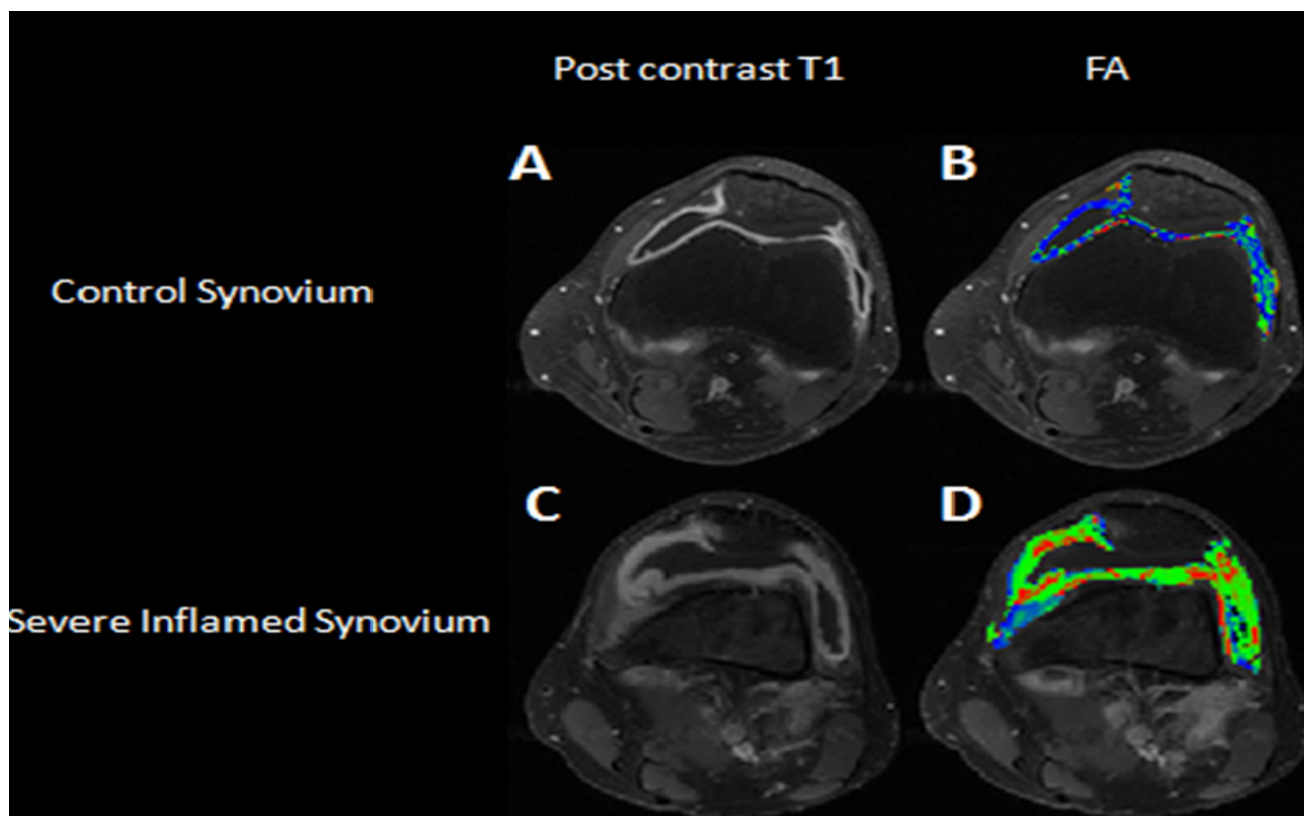
IL-1 beta   TNF-alfa

Fig 4: Knee joint of patient with rheumatoid arthritis (RA) and healthy control showing DTI metrics in segmented region of enhanced synovial membrane on postcontrast T1-weighted image.

A - postcontrast T1-weighted image showing synovial membrane of healthy control, B - RGB color map of FA healthy synovium, C - postcontrast T1-weighted image showing enhanced synovial membrane of rheumatoid arthritis patients, D - RGB color map of FA of RA synovium

Increased uptake of [18F] FDG is mediated through glucose transporters type 1 (GLUT1) and type 3 (GLUT3), which are overexpressed on the cell surface of hypermetabolic cells. [18F] FDG is rapidly phosphorylated to [18F] FDG-6-phosphate by hexokinase. This molecule is effectively trapped intracellularly, as it cannot be metabolized furthser.[49]

A number of studies have reported increased uptake of [18F] FDG-PET at clinically inflamed joints.[50, 51] A study by Goerres *et al.* have demonstrated that the quantitative uptake of 18F-FDG correlated with levels of inflammatory markers.[52] Another study conducted using the 11C-(R)-PK11195 tracer, which binds to peripheral benzodiazepine receptors on macrophages, showed that tracer uptake was significantly higher in severely inflamed joints than in normal joints. Tracer uptake correlated with peripheral benzodiazepine receptor staining on macrophages in the synovial sublining and also with CD68 staining.[53] It has been proposed that PET techniques could be used for imaging sub-clinical synovitis, because of their sensitivity and ability to capture many joints.

A more recent 18F-FDG whole-body PET study was performed in 18 RA patients, among them four were in clinical remission.[54] The results demonstrated that all parameters measured at the large joints were significantly lower in remission patients. In another study, anti-TNF therapy led to decrease in 18F-FDG uptake in the inflamed joints and decreased in the CRP and matrix metalloproteinase-3 (MMP-3) levels.[55, 56] Gent *et al.* used [11C] PK11195 PET to detect sub-clinical joint inflammation in a group of 29 anti CCP-positive patients with arthralgia (pre-RA).[57] Small joints of the hands and wrists were assessed for tracer uptake and scored 0-3 for each joint. PET-positive joints were found in four patients at baseline and within 2 years of follow-up, and all had developed RA. Another five patients who were scan-negative at baseline also developed clinical RA. Three of them reported joint involvement outside the PET field of view. However, PET is unlikely to have practical applications in the monitoring of treatment response in RA as the radiation dose of a PET-CT scan is of the order of 10 mSv (or 500 chest X-rays) and repeating this over time would be unacceptable.

Conclusion

Various imaging techniques are rapidly emerging as a powerful tool that can help elucidating the pathophysiology of synovial inflammation and cartilage disturbances that occur in various forms of arthritis. Non-invasive techniques like MRI, ultrasonography, PET, and bone scintigraphy are used in routine clinical practice to assess the inflammation in the joints. Although US is beneficial in detecting thickening of the synovial membrane and Doppler imaging to reveal increased synovial blood flow, cellular infiltration within bone remains invisible. Ultrasonography, though rapid and easy to perform, is less sensitive and highly operator dependent. Similarly, bone scintigraphy is less specific. Though PET is highly sensitive, it is still experimental. The MRI scoring system is highly complex, as it is based on the sum of the scores for erosions, bone marrow edema, synovitis, and tendinitis at several areas within the wrist. Moreover, the technique is very time consuming, and needs to be performed by experts to obtain reproducible results. But all these new emerging imaging techniques have clinical implication in different clinical scenarios to detect and quantify synovial inflammation and vascularity and changes in cartilage biochemistry. These techniques may also assist in evaluating the clinical efficacy of disease modifying pharmacologic agents.

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