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MINIREVIEWS

Quantifying synovial inflammation: Emerging imaging techniques

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Abstract

Imaging techniques to assess synovial inflammation includes radiography, ultrasound, computed tomography, magnetic resonance imaging (MRI) and recently positron emission tomography. The ideal objective of imaging approaches are to quantify synovial inflammation by capturing features such as synovial hyperplasia, neo-angiogenesis and infiltration of immune cells in the synovium. This may enable clinicians to estimate response to therapy by measuring the improvement in the inflammatory signals at the level of synovium. Ultrasound can provide information regarding thickening of the synovial membrane and can reveal increased synovial blood flow using power Doppler technique. Bone marrow edema and synovial membrane thickness on MRI scan may serve as indicators for arthritis progression. Enhancement of the synovium on dynamic contrast MRI may closely mirror the inflammatory activity in the synovium. Diffusion tensor imaging is an advance MRI approach that evaluates the inflammation related to cell infiltration or aggregation in an inflamed synovium. In this review, we summarize the newer imaging techniques and their developments to evaluate synovial inflammation.

Key words: Synovitis; Imaging; Diffusion tensor imaging; Positron emission tomography; Computed tomography; Ultrasound

Core tip: Nowadays, more and more emphasis is being put on capturing the microscopic features of inflammation on non-invasive techniques of imaging. Emerging magnetic resonance imaging techniques seem to have potential to capture these molecular events and replace synovial histology in future. In this paper we have reviewed exciting recent advances in the field of imaging that pick up inflammatory signals from inflamed synovium and are likely to be available for routine clinical practice in near future.

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INTRODUCTION

In chronic inflammatory joint diseases, synovium is the major site of inflammation. During inflammation, the phenotype of synovium is modified and it changes into thickened invasive tissue that erodes into surrounding soft tissues (cartilage, ligaments and tendons) and bone tissue. It is difficult to define the stages during the transformation of non-specific synovitis into aggressive invasive destructive synovitis[1]. Infiltration of macrophages in the synovial membrane is of pathogenic importance because macrophages generate several pro-inflammatory cytokines for example interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) activate synovial neovascularisation and cause damage to joint by various mechanisms[2]. Greater understanding about the pathogenesis of

synovial inflammation has led to development of focused biologic treatments that minimize disease progression and tissue destruction. Development of biologics such as anti-TNF-α monoclonal antibodies, antibodies against IL-6, receptor activator for nuclear factor-κ B ligand, IL-17 and CD20 (B cell) improve arthritis symptoms by reducing the synovial inflammation[3]. The full-benefits of newer treatments can only be noticed if tools are available to perfectly identify the site and severity of synovial inflammation before irreversible damage occurs. In this review, we focus on the current improvements in imaging modalities as well as how these newer imaging modalities can be applied in the monitoring of synovitis and application of these newer imaging modalities in effective control of synovial inflammation in various arthritic disorders.

RADIOGRAPHY

Virtually all patients undergo radiographs or X-rays of the joint at initial presentation to know the extent of the disease and damage to the joints. Sequential image analysis is commonly executed during the treatment to monitor synovitis progression or regression (erosion scores or joint space narrowing). It has following advantages; easy availability, extensive image acquisition of almost all the joints areas, latest digitised formats grant simple restoration and evaluation of images in future and comparatively very economical. Drawbacks include contact with ionising radiation, which is however comparatively low for one time of X-rays but can become high over a period of time during sequential X-rays[4] and, most significantly, a lack of sensitivity in detecting early synovial inflammation and early joint damage[5,6].

X-ray in synovitis progression

Plain X-rays are not beneficial in monitoring of progression of synovitis in early arthritis patients. X-rays of wrist and knee joint are abnormal in 15%-30% of patients at initial presentation who finally fulfils the diagnostic criteria of rheumatoid arthritis (RA)[7]. In early RA, radiographs reveal non-specific synovial thickening and periarticular osteopenia, neither of which is diagnostic. However, in late RA characteristic erosions and their pattern of joint involvement may suggest diagnosis of RA but by then disease is far advanced. Despite this fact, radiographs have been extensively validated in a number of clinical trials. In ATTRACT (Anti TNF Therapy in RA with Concomitant Therapy) study, examining the effectiveness of infliximab in preventing progression of joint erosions[8], the two radiologists had a high reliability with correlations varying between 0.84 at baseline to 0.92 at weeks 102 of total radiographic scores. However, radiographs provide a very little information regarding severity of inflammation and lacks quantifiable variables of inflammation in early arthritis. They are reliable indicators of damage.

ULTRASONOGRAPHY

Latest reports recommend that ultrasonography (US) may be an important imaging technique to determine the degree of synovitis in active RA joints. Furthermore, it may be more sensitive in identifying active synovial inflammation than clinical joint examination[9]. Recently, Le Boedec *et al*[10] reported that US may provide additional useful information beyond clinical joint examination in the shoulders and metatarsophalangeal joints. They further concluded that the usefulness of power Doppler and B mode ultrasound were reduced with low DAS28 score and shorter disease duration respectively[10]. US can provide information about disease activity (synovial inflammation and tenosynovitis) and joint damage (bone erosions)[11]. Hence, US not only may help in examination but may also help in monitoring outcome of treatment. Ultrasonic waves when hit the tissue interfaces, they are reflected back and these reflected waves (echo waves) are recorded to generate US images. Thickness of synovium in areas of joint capsule and tenosynovium can be detected by B mode grey scale US (GSUS)[12]. Synovial inflammation in the knee of RA patients was examined through GSUS at 5.0 MHz in a study evaluating Yttrium-90 radiation synovectomy[13]. In this study GSUS findings (suprapatellar effusion and synovial thickening) correlated well with the clinical and arthrographic findings.

US imaging approach is even more enhanced with the application of Doppler techniques[14]. Flow of red blood cells, either towards the US probe or away from it, demonstrated by Colour Doppler US is suitable for analyzing excessive flow rate in blood vessels[15]. Hypertrophy of the synovium is determined as non- displaceable, intra-articular, poorly compressible, which can be recognized by Doppler signal[16]. Thickened synovium is much less compressible therefore on probe compress fluid movement is very less while in normal synovium fluid is displaced easily on probe compression. Sometimes, normal anatomical tissues may mimic synovial inflammation due to low reflectivity of US waves, particularly with US equipment of lower resolution[17].

Power Doppler US (PDUS) is the most beneficial US technique in rheumatology. It analyses Doppler changes of the moving red blood cell, regardless of its route and rate, and is consequently well developed for the quantification of blood flow rate within the low flow synovium[18,19]. PDUS can quantify inflammatory activity in the erosions of RA by revealing increased blood flow in the synovium of these patients. Histological analysis have confirmed that changes in power Doppler signals are associated with inflammatory changes in the synovial membrane[20], however one must be cautious about artefact signals at bone synovium interface especially if gain setting of the US machine is high. Increased Doppler signal matches specifically with neutrophils recruitment and area fibrin accumulation[21], however, no exact correlation between systemic vascular endothelial growth factor expression and neo-vascularisation was demonstrated. PDUS is sensitive but also more vulnerable to false signals. The software that measures PDUS is proprietary; therefore, results from one manufacturer may not be comparable with another.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a sensitive image acquisition technique that depends on ion emitting isotopes of radioactive element. Positron loses energy after it collides with atoms and is exhausted after colliding with an electron, leading to the emission of two gamma rays. After collision two gamma rays travel in opposite direction. The PET sensor captures signal of these two energy packets (photons) along with their relative position. PET sensors at the same time capture signal of these energy packet from various directions. Associated computed tomography (CT) scanning offers superior structural information of the tissues and spatial localization of the PET signals. A tracer molecule fluorodeoxyglucose [(18F) FDG] has been widely used in PET research. It has homology with the sugar molecule but it contains radioactive isotope, upon accumulation in the metabolic active cells it gives the signal which is captured by PET scanning and provide information about the location of inflamed tissue. Increased uptake of this sugar analogue is directed by the various sugar transporter receptors such as GLUT1 and GLUT3 on the cell surface, both are over expressed on hyper metabolic cells. This sugar analogue is phosphorylated by the hexokinase enzyme but it is not metabolised further in the glycolytic pathway and is trapped in the cells[22].

Several attempts with the FDG PET in the estimation of synovial inflammation in arthritis demonstrated that there is enhanced uptake of 18F-FDG in the inflamed synovium[23,24]. The semi-quantitative scoring of joint involvement and quantitative uptake of 18F-FDG has been shown to correlate with markers of inflammation[25]. Another tracer molecule 11C R PK11195 has also been used in PET scanning which specifically binds to the receptors present on phagocytic cells. This group analysed joint of 11 inflammatory arthritis individuals and examine the joints with the invasive methods such as arthroscopic surgery and histology[26]. It was observed that tracer molecule accumulation was higher in inflamed joints as compared to non- inflamed joints of the same individual. The uptake of tracer molecule correlated well with expression of benzodiazepine receptor and CD68 expression on macrophages in the synovium. Being highly sensitive and ability to capture multiple joints simultaneously, PET scan may be used to pick up sub clinical synovitis. Recently, PET analysis with 18F FDG tracer molecule was conducted in 18 inflammatory arthritis patients; four of them were in disease remission status[27]. 18F FDG uptake was significantly different between patients with active RA vs patients in remission. Moreover, it has been reported that 18F FDG uptake varied with alterations in CRP and matrix metalloproteinase 3 levels in patients with RA receiving anti-TNF therapy[28,29]. However, as radiation amount of a PET-CT is high, it cannot be recommended for routine screening of RA patients in clinical practice. To overcome this problem, a new technique, PET MRI is being developed[30]. Currently, there is no data available regarding its role in evaluation of synovial inflammation. Synovial phagocytes cell were targeted with tracer molecule PK11195 in PET scanning to identify early synovial inflammation in 24 anticyclic citrullinated peptide antibody positive patients presenting with arthralgias only. PET scan was focused on hand joints only. Four patients were detected to have PET positive joints at baseline and all four developed RA within next 2 years. Amongst rest, five more developed RA but had negative PET scan at baseline. Among these five two developed arthritis of hand joints and rest three developed arthritis outside the field of view of PET scanner[31].

CT SCANNING

Compared to other imaging approaches very few CT scan based investigations are available in the context of synovial inflammation. It may assist in diagnosis of several different kinds of inflammatory arthritides. Similar to conventional X-ray, it very well demonstrates the cortical bone architecture and is considered as the gold standard for the imaging of erosions in the joints against which other imaging techniques are evaluated[32-34]. Multidetector CT generates quite excellent images which can be saved in a digital format and can be utilized to compare progression of the joint erosions during follow up. CT scan out-performed MRI in evaluating joint erosions at wrists in RA[34]. Similar data was reported by Døhn *et al*[35,36] for erosions at the metacarpophalangeal (MCP) joints during serial monitoring of patients of RA being treated with anti TNF-α therapy. CT scanning exposes to ionising rays but the influence of this is comparatively minimal as only the extremities are analysed. The major drawback of CT scanning is limited coverage of joint areas as compared to conventional X-ray imaging[37].

Micro focal CT is a better image quality strategy which enables assessment of bone mineral density. This technique has been used for the analysis of erosions in RA. In a study it was observed that small erosions in joints were seen in both controls and RA subjects, but erosions > 1.9 mm diameter were specific for RA. Using this very technique it was reported that anti interleukin 6 receptor monoclonal antibody (tocilizumab) could repair bone erosions and has favourable effect on bone remodelling in RA[38,39].

CT osteoabsorptiometry is another imaging strategy which has been utilized to evaluate periarticular osteopaenia in early inflammatory arthritis. It was observed that RA patients had significantly less mineralization at MCP joints compared to control subjects[40]. Volumetric bone mineral density evaluated with the use of a quantitative CT (high resolution-peripheral quantitative CT, HR pQCT) system confirmed the involvement of trabecular bone compartment in the peri-articular osteopenia[41]. Presently, all these newer CT scan techniques are only at research stages and are less likely to be available for routine clinical practice in near future.

MRI IN SYNOVITIS

MRI is one of the most sensitive methods available to evaluate cartilage, synovium and bone tissue changes in the joint. MRI-based quantification of synovial thickening and synovial fluid volume indicate disease activity. The signal strength related with synovial thickening is intermediate to minimal on T1 weighted image, but higher on T2 weighted image due to excessive water of synovial fluid within the synovium and reflects the degree of inflammation[42]. Synovial inflammation is further enhanced on T2 weighted image on MRI scanning. Differentiation of synovial inflammation from synovial fluid without using contrast agent is challenging; however, heavily T2 weighted images can differentiate between the two. Compared to joint effusion inflamed synovium has lower signal intensity on T2-weighted image[43]. Contrast based T1 enhancement on MR imaging with kinetic study is helpful in differentiation of effusion from inflamed synovium[44,45]. Gadolinium based contrast medium enhances inflamed synovium soon after administration however, it rapidly diffuses into synovial fluid compartment, resulting in equal signal strengths between synovium and the synovial fluid. This rate of equilibration of signals between the synovium membrane and the synovial fluid compartment may indicate the degree of leakiness of inflamed vessels in the synovium and thus intensity of inflammation[45].

Dynamic contrast enhanced MRI in synovitis progression

Dynamic contrast enhanced MRI (DCE MRI) is an imaging technique which is used for evaluation of the pharmacokinetic factors relevant to the exchange of contrast material between intravascular and extra vascular spaces and indicate the presence of new blood vessels (neo angiogenesis) in inflamed joint. T1 weighted MRI images are obtained prior to and after administration of a T1-shortening diffusible contrast agent. Post contrast time intensity curve delineating the concentration of the contrast agent in the areas of synovium reflects the intensity of inflammation in the synovium. Information obtained from the time intensity curve can be examined semi quantitatively or quantitatively with the Toft's model based software. In the semi quantitative analysis, factors that define the form of the time intensity curve, for example uptake of contrast agent, maximum enhancement and wash out ratio are calculated[46-49]. The degree of synovial inflammation is quantified by pharmacokinetic model by plotting time intensity curve which analyses diffusion of contrast agent from the vascular compartment to the extra vascular extracellular compartment[46]. The rate of exchange of contrast agent between these two compartments and amount of contrast agent in the extracellular spaces depend upon the perfusion and leakiness of the blood vessels in the synovium. DCE MRI is being progressively utilized for the recognition of synovial inflammation in early inflammatory arthritis. DCE MRI results have been correlated strongly with histological severity of inflamed knee synovium. Not only this, it was further utilized to monitor reduction in inflammation following intra articular steroid injection[50-52]. Another study reported that many RA patients display enhanced capillary leak and vascularisation of the synovium[53]. Efficacy of antiTNFα treatment in RA patients was observed by decrease in various DCE MRI parameters such as enhanced T1 relaxation time, volume transfer constant and fractional blood volume. Furthermore, volume transfer constant (kp) has been reported to be a good marker of vascularity in the synovium[49]. In other studies in RA patients, color coded DCE MRI parameters such as; micro vessels density and permeability were overlapped over anatomical MRI images, it was observed that the distribution of information produced by kps and fractional blood volume computations matches the qualitative evaluation of signal strength on post contrast T1 images[46,49]. Analyses of qualitative readings of colour coded parametric images were reliable and consistent on several image acquisitions of the same individual at different time intervals. Hence, DCE MRI represents a highly efficient technique which has potential to be non-invasive imaging biomarker for evaluation of alterations in vascularity of inflamed synovium. It can be utilized for monitoring efficacy of disease-modifying anti-rheumatic drugs (DMARD) and biologic therapies in RA and other inflammatory arthritis.

Advantages and disadvantages of various imaging techniques have been listed in Table 1.

Quantify synovial inflammation with diffusion tensor imaging

Diffusion tensor image (DTI) is a non contrast based image strategy that quantifies diffusion of fluid in vivo as well as provides details of the tissues at microscopic level[54,55]. This imaging strategy has been used in the evaluation of structure of organised tissues such as neural tissues of the brain, heart muscle tissues and intervertebral disc[56]. Because of presence of the cell membranes and other elements in *in vivo* system, diffusion of water molecules is restricted and these arrange themselves along a particular direction, along the length of tissue components rather than perpendicularly, on application of strong magnetic field. Restricted movement of water molecules in a particular direction is called as anisotropic diffusion. Anisotropy of water molecule can be utilized to obtain details about the cells organization at microscopic level[57]. Diffusion of normal fluid is isotropic and it can be analyzed with only one diffusion parameter but in biological tissue anisotropic diffusion can be described by a 3 × 3 symmetric matrix. In biological tissues, complete diffusion matrix can be computed by calculating 6 independent matrix elements. The most widely used scalar indices that are based on DTI are the fractional anisotropy (FA) and mean diffusivity (MD)[58-60]. FA is a measure of diffusion anisotropy and its minimum value "0" represents isotropic diffusion, *i.e.*, equal probability of diffusion in all directions. Whereas a maximum value of "1" represents highly restricted diffusion such as very thin fibres. MD on the other hand represents mean of

Table 1 Comparison of various non-invasive imaging techniques in assessment of synovial inflammation

Imaging technique for quantification of synovial inflammation	Advantages	Limitations
Radiography	Cost effective, Ease of access, Wide coverage of important joint regions, newer digitised formats that allow easy retrieval and comparison of images longitudinally and relative low cost	Exposure to ionising radiation, which although relatively low for one set of X-rays can cumulate over time with a potential impact on patient longevity Lack of sensitivity for detecting early joint damage and inability to image the inflammatory processes within the joint that precede damage Very little information regarding severity of inflammation Lacks quantifiable variables of inflammation in early arthritis
Ultrasonography	It is sensitive, cost effective, can be performed by the treating physician in out-patient-department basis, and can be repeated as desired for serial monitoring of inflammation	Normal anatomical structures may have low reflectivity and mimic synovitis if careful attention is not paid to technique, particularly with lower resolution equipment Operator dependent
Positron emission tomography	Sensitive, able to assess inflammation at molecular level Used for imaging sub-clinical synovitis because of their sensitivity and ability to capture many joints	Costly, Still experimental No evidences available in early synovitis. Not available at many centres and not being used in day to day clinical practices High radiation exposure
Computed tomography scanning	Cost effective Multidetector helical CT produces very high-quality images which can be stored in a digitised format and compared with later images to determine erosion progression Gold standard for imaging of bone erosions	Computed tomography scan upon whole body scanning leads to high dose radiation exposure It does provide less coverage than plain radiography as usually only one joint area is scanned
Magnetic resonance imaging	Sensitive techniques to assess soft tissue and bone changes in the joints Very sensitive for the detection of early synovial inflammation Diffusion Tensor based imaging can evaluate molecular event during synovial inflammation without contrast medium	Time consuming, Relatively costly Contrast based enhancement required for dynamic study

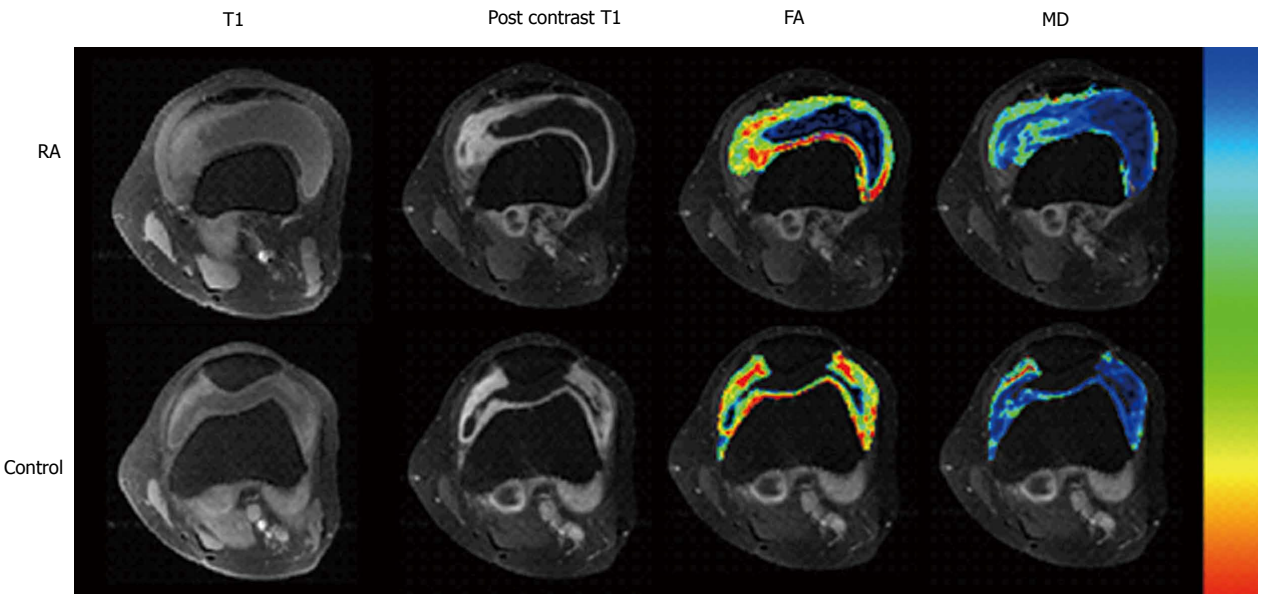

Figure 1 A 45-year-old male rheumatoid arthritis synovium shows strong enhancement on fat suppressed post-contrast T1-weighted axial image. Color coded fractional anisotropy (FA = 0.26) map from segmented region of enhanced synovial membrane overlaid on post-contrast fat-suppressed T1-weighted image show increased FA as compared to control (FA = 0.19). Mean diffusivity being inversely related to FA showed low values (1.01×10^{-3} mm^2/s). Color red denotes increased whereas blue denotes decreased values. RA: Rheumatoid arthritis; MD: Mean diffusivity; FA: Fractional anisotropy.

molecular motion independent of direction of the tissue. It depends upon the size and integrity of the cells.

We have earlier evaluated DTI parameters to assess severity of synovial inflammation in eighteen RA patients and six healthy individuals. Considerably significant high FA and reduced mean diffusivity were seen in RA individuals in comparison to controls (Figure 1). In this study we found a strong association between FA and synovial liquid IL-1β and TNF-α levels[61]. We also observed a positive correlation between cylindrical isotropy and

sICAM which suggested that the adhered inflammatory molecules on synovium represent the planar model of diffusion tensor. This led us to speculate that limited movement of water molecule in the synovium of inflammatory arthritis patients was a consequence of inflammatory cell infiltration and aggregation[62]. It has been suggested that this technique may replace synovial histology to evaluate the severity of inflammation and assess efficacy of disease modifying drug therapy[63].

CONCLUSION

Various newer imaging techniques are being utilized to explore the pathogenesis of synovial inflammation and soft tissue disruptions that occur in various inflammatory and damaging arthritides. The new emerging techniques have capability to quantify synovial inflammation and vascularity and modifications in cartilage biochemistry as well. A combination of DTI with DCE MRI may capture microscopic features of inflammation such as cellular infiltration and increased vascularity and may emerge as powerful tools to evaluate severity of inflammation at the level of synovium. These imaging strategies are important for analyzing the clinical effectiveness of DMARDs and biologics. Developments in imaging techniques, such as the miniaturization of extremity magnet for DCE and DTI MRI, and automated software programs may make these techniques available for routine clinical usage.

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