Advanced Imaging in Osteoarthritis

David J. Hunter, M.B.B.S., Ph.D.

Abstract

Historically plain radiography has been the primary investigative tool by which structure in osteoarthritis is measured. Magnetic resonance imaging (MRI) is widely used in medical diagnosis for its various advantageous features, such as high-resolution capability, the ability to produce an arbitrary anatomic cross-sectional image, and wide range of available tissue contrast. Its ability to image features such as the subchondral bone, cartilage and soft tissue structures means that its application in knee osteoarthritis (OA) raises hope of improving our understanding of structural associations of pain and function in OA joints, previously based on conventional radiography. Additionally, MRI has the potential for assessing the effect of risk factors for epidemiologic investigation and the effectiveness of therapeutic interventions in OA clinical trials.

Osteoarthritis (OA) is a significant public health challenge and is ranked as the leading cause of disability in elders. OA affects an estimated 21 million Americans. Recent estimates suggest that symptomatic OA of the knee occurs in 6% of adults 30 years of age and older and in 13% of persons age 60 and over. Despite being extraordinarily prevalent, OA remains a condition that is poorly understood and a condition for which few effective therapeutic options are available. Therapeutic development in OA is constrained by the slow progression of the condition, its heterogeneous clinical manifestations, and the need for long-term follow-up to observe changes in structure. There are new technologies that may improve the assessment, early development, and progression of OA, and greatly facilitate clinical and epidemiological research. Foremost among these is magnetic resonance imaging (MRI), a sensitive, noninvasive method for assessing joint morphology.

Magnetic Resonance Imaging

MRI is ideally suited for imaging arthritic joints, as it is free of ionizing radiation, and its tomographic viewing perspective obviates morphological distortion, magnification, and superimposition. More importantly, however, MRI has unlimited image contrast variability, resulting in an unparalleled ability to identify articular tissues, such as cartilage, menisci, bone, synovium, and ligaments. This technology, therefore, holds the greatest potential as a tool for whole-organ imaging of the OA joint; an attribute which allows for whole-organ assessment that could help discriminate different patterns of intra-articular involvement in OA.

While MRI has enormous potential, methods of analyzing MRI images of joints are in their infancy. For example, semi-quantitative scales, such as the Whole Organ MRI Score (WORMS) and the Boston-Leeds Osteoarthritis Knee Score (BLOKS), are used to score multiple features in joints. The value of these scales notwithstanding, an in-depth evaluation of each of the joint features may reveal informative findings that would be missed by global scales. Also, the volume of cartilage in large plates is summarized, whereas clinically relevant changes may occur at a sub-plate level. It may be that following focally denuded areas or focal partial-thickness lesions will be more responsive than ascertaining the change in volume of the whole compartment (a measure that is confounded by multiple factors). Metaphyseal enlargement with age and OA might create problems for a measure of cartilage morphometry (such as cartilage volume) that did not adjust for bone size. Early osteoarthritic cartilage may not be thin but rather thick and swollen with water that is imbibed by cartilage when the collagen network is disrupted and the role of proteoglycans is altered. The responsiveness of dif-
ferent measures of cartilage morphometry and their construct validity needs to be explored to answer which of the plethora of morphometric measures available should be recommended for use in clinical trials.

Thus, MRI is providing insights into the relationship of structure to function and will continue to evolve with advances in measurement science to facilitate improved detection of change. These advances in the use of MRI for clinical studies of OA depend on continued investigation of the measurement of each feature in the joint that is imaged, not just the hyaline articular cartilage. The purpose of this review is to briefly consider radiographic developments, appraise the developments in MRI as it pertains to OA, and suggest where further development may best be applied.

Plain Radiography
In OA of the knee, cartilage is lost slowly, often over decades. The rate of loss is thought to be highly variable across individuals. Traditionally, this process has been characterized using radiographs and often classified by the Kellgren and Lawrence (K&L) grading system; a system that is heavily dependent on the osteophyte for classification of disease. Due to inherent limitations, individual grading systems for different features, including osteophytes and joint space narrowing (JSN), have been developed. Observational studies using these grading systems have demonstrated that, while the odds of knee pain increase with increasing radiographic severity (more so for osteophytes than JSN), the relation between radiographic structural change and pain and function in OA is not strong. Further confounding this relation, recent data suggests that knee pain itself can modify the measurement of joint space width in weightbearing extended-view radiographs.

Preventing cartilage loss has increasingly become the goal of drug development in OA. Measurement of the rate of loss of cartilage in individuals in a reproducible and sensitive manner is highly advantageous when assessing progression in individual patients. Standardized techniques for measuring joint space width (JSW) in the medial tibiofemoral (TF) compartment, taken from carefully acquired radiographs, have become accepted for quantifying changes in TF articular cartilage thickness in knee OA. Recent analyses would suggest that the better the positioning in terms of tibial rim alignment, the better the opportunity to detect change. There remains, however, considerable controversy over the preferred method of knee radiographic acquisition and JSW measurement.

Imaging Structural Changes in Hyaline Articular Cartilage in Osteoarthritis
Although many joint structures are affected, OA manifests prominently in the articular cartilage. The medial compartment of the knee is the most common site of involvement in knee OA, and has been the subject of the majority of previous studies in this context. Traditionally, the progression of knee OA has been assessed by measuring changes in the width of the space between the medial femoral condyle and medial tibial plateau on plain radiographs. A reduction in the thickness of the radiolucent articular cartilage layers between the bones is inferred from a reduction in this space. Radiological methods for measuring JSW have been refined in recent years but remain technically challenging, particularly within the context of a large multicenter trial. As well, they have poor test and retest precision, even with appropriate use of standardized techniques. Measurement errors due to variability in participant positioning mean that considerable effort needs to be expended for standardization, including the use of fluoroscopic knee positioning, which exposes participants to higher levels of radiation. Recent data suggests that progression in JSW loss is further confounded by changes in joint tissues other than the articular cartilage, particularly, the menisci. Furthermore, these techniques are applicable to only the medial compartment. These limitations, together with the requirement for some remaining joint space, greatly restrict the wider applicability of this measure.

Although MRI has not been formally accepted by regulatory authorities, many experts now agree that MRI may be an improved imaging technique for monitoring progression of OA in the knee. For example, there is a significant body of supporting data on the longitudinal change in cartilage volume as a preferred primary end point to reflect OA progression. Several other quantitative MRI end points have also been investigated, although there is less experience and more limited validation with these. MRI of the knee can directly visualize hyaline articular cartilage and cover the whole joint in one examination, meaning that the cartilage defects in the joint can be visualized directly, regardless of their location.

Methods of MR Image Analysis
Broader speaking, MRIs of OA features can be measured semi-quantitatively or quantitatively, or compositional measurements of articular cartilage can be obtained. This review will focus on semi-quantitative measurement and quantitative measures; however, basic features regarding each are as follows:

1. Observer dependent semi-quantitative image analysis. Semi-quantitative scoring of MRIs is a valuable method for performing multi-feature assessment of the knee, using conventional MRI acquisition. Such approaches score, in an observer dependent semi-quantitative manner, a variety of features that are currently believed to be relevant to the functional integrity of the knee or that are potentially involved in the pathophysiology of OA, or both. These articular features can include articular cartilage integrity, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, marginal and central osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis and effusion, intra-articular loose bodies, as well as periarticular cysts and bursitis.
These instruments for scoring MRI on OA have shown adequate reliability, specificity, and sensitivity, as well as an ability to detect lesion progression over 1 to 2 years. At the present time, the limited longitudinal data on these scoring systems, compared to cartilage volume measurement, somewhat precludes their use as primary outcome. However, the ability to measure individual characteristics of OA has considerable appeal in delineating structural risk factors for both pain and progression.

2. Quantitative measurements using computer-aided image processing to assess whole joint quantification (cartilage, bone, synovium, etc.). Three-dimensional (3D) coverage of an entire cartilaginous region by MRI allows for the direct quantification of cartilage volume. Quantitative analysis of cartilage morphometry from MRI is becoming more widely used for the assessment of OA.

Measurements of cartilage volume via MRI previously have been shown to correlate well with the ex vivo assessments of cartilage volume (stripped away from bone). The measurement of cartilage volume provides quantitative data with which to monitor the progression of OA. Such data could be beneficial not only in the assessment of risk factors and for longitudinal monitoring of the OA, but also in the evaluation of potential therapeutic agents. An important aspect of many quantification methods for cartilage volume is the accurate segmentation of cartilage from surrounding tissues. The ideal segmentation strategy is one that produces accurate and precise results in a reasonable amount of time with minimal subjectivity. The most widely used method is manual tracing, whereby an operator on a computer workstation freely draws a boundary on an image to indicate the location of an object. The process of manually locating the boundary, while straightforward, can be time-consuming and subject to operator bias and error.

Automated methods, such as those based on edge-detection, can quickly segment the cartilage with little or no user interaction by using signal intensity information. An example of a partially automated method is a region-growing algorithm that determines cartilage volume based on neighborhood connectivity, starting with an operator-placed seed pixel. However, automated methods (without the aid of a human operator) are vulnerable to poor image contrast and low signal-to-noise ratio (SNR), which can result in grossly inaccurate positioning of the cartilage boundary.

User-driven segmentation methods combine the sensibility of a human operator in the recognition of the object boundary with the reliability of a computer to quickly, and, in a manner that is reproducible, delineate the boundary. In an implementation of a user-driven segmentation strategy, an operator guides the recognition of the boundary, and the computer performs the delineation based on information gathered from image data. Examples of such methods include deformable contours using B-spline snakes, active contours, and active shape models. Not only can cartilage morphology be quantitatively assessed but other structures can be as well, such as bone marrow lesion (BML) volume and synovial volume. An example of a segmented cartilage map from the knee is depicted in Figure 1.

3. Compositional measures of articular cartilage. While quantitative measurement of morphology can be used to monitor loss of cartilage tissue, there is interest in using MRI to detect changes that precede gross tissue degradation. Applications of parametric mapping techniques sensitive to early cartilage damage have been addressed in recent reviews. These methods include T2 mapping, dGEMRIC, and T1rho and are extensively reviewed elsewhere.

Validity and Reliability of Quantitative MRI-Based Cartilage Measurements

Up to the present day, no generally accepted medical therapy is available for preventing cartilage loss in OA. However, a number of putative therapeutic agents and surgical procedures that are currently under development show great promise in this regard. These advances have renewed the hope of one day controlling the progression of this debili-
tating disease. An important obstacle to development has been the absence of validated, noninvasive, and responsive methods of quantifying articular cartilage.

An OMERACT-OARSI (Outcome Measures in Rheumatology Arthritis Clinical Trials-Osteoarthritis Research Society International) workshop on imaging technologies with scientists and clinicians from academia, the pharmaceutical industry, and the regulatory agencies has published a comprehensive review of the collective published and unpublished data concerning: 1. MRI pulse sequence considerations for morphological analysis of articular cartilage; 2. techniques for segmenting cartilage; 3. semi-quantitative scoring of cartilage status; and 4. technical validity, precision, and sensitivity to change of quantitative measures of cartilage morphology. Among their conclusions was that quantitative assessment of cartilage morphology, with fat-suppressed gradient echo sequences, and appropriate image analysis techniques, displays high accuracy and adequate precision (e.g., root-mean-square standard deviation medial tibia equals 61 μm³) for longitudinal studies in OA patients. Longitudinal studies suggest that changes of cartilage volume of the order of -4% to -6% occur per annum in OA in most knee compartments (e.g., -90 μm³ in medial tibia). Annual changes in cartilage volume exceed the precision errors and appear to be associated with clinical symptoms, as well as with time to knee arthroplasty.

Validation of cartilage volume and thickness measurements have been carried out in cadaver knee joints and in patients prior to knee arthroplasty in a number of studies. Most of these document a close linear relationship between the two measures, with differences in the range of 5% to 10%. MRI cartilage volume and thickness measurements obtained prior to arthroplasty have been validated against actual cartilage volume from the resected specimen. Cartilage volume assessments were lower using MRI (range, 7% to 27%), but there was a high correlation between the two measures (r = 0.98; standard error, 7%).

This study provided estimates of absolute cartilage volume loss, e.g., mean medial tibia cartilage loss in patients with medial compartment arthroplasty was 1290 mm³.

The in vivo reproducibility (intraobserver, inter-scan, image acquisition in one session) of cartilage volume measurements also appears to be excellent. Earlier cohorts had slightly higher coefficients of variation (CVs) than more recent studies where the CVs range from approximately 1% to 3%.

MRI assessments of OA severity appear clinically relevant and have discriminative validity. Comparison of cartilage volume measured by MRI with severity of radiographic JSN showed a mean reduction in tibial cartilage volume of 1.00 ml (sd, 0.32) in the medial compartment and 0.53 ml (sd, 0.25) in the lateral compartment for each increment in JSN score. Estrogen users were found to have more cartilage than non-users [adjusted difference equaled 0.30 ml; 95% confidence interval (CI), 0.08 to 0.52]. MRI can detect alteration of cartilage thickness with activity and is more sensitive in assessment of OA progression than radiography and arthroscopy. Cartilage volume is weakly associated with symptoms, and there is some suggestion that it predicts arthroplasty.

### MRI Studies Evaluating Longitudinal Change in Cartilage Volume

Currently, there are a large number of publications describing the longitudinal measurement performance of cartilage volume among clinical cohorts followed for periods of up to 3 years. With one exception, these studies show progressive cartilage volume loss, with a mean value in the medial tibia, of ~5%, an sd of ~5%, and a range of 3.8% to 7.4%. One study detected cartilage volume loss in the absence of change in radiographic JSW, suggesting that MRI has greater sensitivity to change than radiography.

The majority of this work comes from one group, which has an observer-based method that allows estimation of cartilage volume. No other morphometric measures (e.g., thickness, percent denuded area) can be computed using their method. In addition, more recent studies have smaller rates of change than those quoted here. The methods in earlier studies differ markedly from more recent studies in that they use a completely manual method of tracing boundaries for segmentation, their analysis is read unblinded to time point order, and they have acquired images using 1.5-T scanners. The more recent studies using similar cartilage quantification techniques demonstrate a cartilage volume loss of about -1% to -3% per year [including mechanical factors in arthritis of the knee (MAK), Pfizer, and, more recently, data from the Osteoarthritis Initiative (OAI)]. These more recent studies generally have found rates of loss similar to what we have found in the medial tibia and femoral plates. If these more recent estimates of cartilage volume change are confirmed, then there are important implications for future clinical trials of disease modifying treatments for OA using MRI techniques.

The design of MRI-based efficacy studies includes decisions on sample size, based on estimations of statistical power derived from prior data or expectations concerning progression. The sample size depends on: 1. the expected rate of progression in participants treated with placebo; 2. the minimum size of drug effect judged to be clinically relevant, or rate of progression expected in the active treatment arm(s); 3. the variation in progression rate that occurs between participants; and 4. the precision of the measurement technique. Variation between participants is a significant driver of study size. For example, detection of a 50% reduction in loss of baseline cartilage volume over 1 year requires evaluable data on 64 participants per arm, if the expected background progression is 5 ± 5%, but 250 per arm if it is 5 ± 10% (for 80% power, alpha is 0.05). Given recent study data, the older literature likely reflects an overestimation of the true rate of change and hence sample size requirements are likely to be even higher.

Thus, conservative study designs based on large MRI
progression series that are currently in the public domain require large sample sizes if cartilage volume is used as the end point. If we could confidently design studies based on either smaller sample sizes or shorter study durations, or both, this would reduce the resource implications for MRI-based interventional studies. It is widely assumed that the use of careful quality control and advanced paradigms for assessing cartilage from raw MRI data will improve measurement precision. Baseline features (such as malalignment, BMLs, or meniscal damage) are also predictive of progression, and it is hoped that these can also be used to increase the study power by selecting participants that have features which predict rapid progression in future studies.

Several studies have suggested that baseline clinical, biomarker, and imaging features are predictive of progression of cartilage loss in the medial compartment of the knee. These include increased body mass index (BMI), an increased level of type II collagen C-terminal degradation products detected in the urine (uCTX-II), the presence of varus malalignment at the TF joint, the presence on MRI of subchondral BMLs, or meniscal abnormalities.

Issues in Interpreting Quantitative Measures in OA MRI

A particular appeal of MRI is the inherent digital acquisition that permits quantification of signal intensities from discrete structures, generation of 3D representations of individual anatomic structures, and computation of their volumes. The technology is being used to provide quantitative measures of cartilage morphometry. Depending on the segmentation approach and the software used, many different morphometric parameters can be measured or derived, including cartilage volume in predefined regions of the knee, thickness and cartilage volume normalized to bone surface area. A description of some of the nomenclature used to describe these measures has recently been described. Unfortunately, while MRI has great promise, there is an ongoing struggle to appreciate its value as a way of defining disease and as a tool to both predict

![Figure 2](image-url) Axial (top row), coronal (middle row), and sagittal images (bottom row) in a patient with knee osteoarthritis: without segmentation (left) and with segmentation of the cartilage (right). Note that the total subchondral bone area is segmented, which is also in areas where the cartilage has been lost (green line). In this way, not only cartilage volume and thickness but also the denuded area can be computed. (Institute of Anatomy and Musculoskeletal Research, Paracelsus Medical University, Austria, under the supervision of Felix Eckstein.)
progression in clinical trials and understand joint symptoms. Further, it is unclear which of the multiplicity of cartilage morphometry measures is most responsive or most valid. Some attempt has been made to develop nomenclature for the regions of the knee and the different measures that can be performed (from volume to thickness to denuded area and beyond). That being said, there is likely great redundancy in many of these measures and the field would benefit from simplifying the terminology. Some of the wealth of available measures is depicted in Figure 2.

A substantial percentage of the variability in cartilage volume is determined by joint surface area. Wang and colleagues demonstrated that the medial and lateral tibial plateau area increased over a 2-year period (2.2% and 1.5% per annum, respectively). Increases at the medial (but not lateral) tibia were stronger in males, in participants with a high BMI, and in subjects with higher baseline grade of medial JSN. Metaphyseal enlargement with age and OA might create problems for a measure of cartilage morphometry (such as volume) that did not adjust for bone size. Variability in cartilage volume is markedly reduced when this measure is normalized to joint surface area, far more, for example, than when cartilage volume is normalized to body weight or body height. Cross-sectional studies suggest this improves discriminatory ability between those with disease versus those without disease. It remains to be seen if this discriminatory ability facilitates distinguishing change within an individual in longitudinal studies.

In early OA, cartilage may not be thin but rather thicker and swollen with water that was imbibed by the cartilage when the collagen network is disrupted and the role of proteoglycans is altered. Thus, measuring cartilage volume in regions of the knee (e.g., medial tibia) and the regional mean thickness, as distinct from focal measures of change (region of interest analysis centered around focal defects), and measures of denuded cartilage, may provide very different measures of change within an individual in longitudinal studies. For every 1° increase in baseline varus angulation, there was, on average, a 257 μl (95% CI, 195 to 321) reduction of the lateral tibia. The same group of investigators also examined the relation between knee alignment and the rate of cartilage loss in subjects with knee OA. For every 1° increase in baseline varus angulation, there was an average annual loss of medial femoral cartilage of 17.7 μl (95% CI, 6.5 to 28.8).

Regulatory Requirements

The U.S. Food and Drug Administration (FDA) developed a guidance document that describes an OA drug development “roadmap.” The document has been in draft format since 1999 (http://www.fda.gov/Cber/gdlns/osteo.htm). The guidance describes a process for drug approval for specific indications in OA, including treatment of symptoms, delays in structural progression, and discussions of the prevention of OA. Radiographic measurement of JSN is currently recommended within the guidance documents of the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) as the imaging end point for clinical trials of disease-modifying OA drugs (DMOADs). At present, an alteration in structural progression would likely be determined by radiographs, but it is possible that newer technologies may include MRI or even ultrasound, once appropriately validated.

Currently, approval of potential therapies in OA requires that the structural alteration of JSN be linked to a clinical benefit, either at the time the structure is measured or at a later time-point. Therefore, with this concept in mind, it is obviously important that improvements in structural features that are part of the OA process be ascertained that are more likely to be linked to clinical symptoms experienced by patients or that alternatively can serve as surrogates for a
clinically meaningful outcome. A surrogate outcome is an end point of a clinical trial and might be an MRI feature that is used as a substitute for a clinically meaningful end point possibly measured directly (determining how a subject feels, functions, or survives). Changes that might be induced by a specific therapy on a surrogate end point would be expected to reflect changes in a clinically meaningful end point. The ultimate clinical benefit could include improvement in pain or function or a delay in the need for a surgical intervention, such as a total knee replacement. Although the use of surrogate outcomes in clinical trials reduces sample size requirements and trial duration, they can only be justified if there is strong evidence that therapeutic targeting of the surrogate will translate into a beneficial patient outcome.\(^6\)

**Imaging Structural Changes in Other Joint Tissues in Osteoarthritis**

Articular cartilage is both aneural and avascular. As such, cartilage is incapable of generating pain, inflammation, stiffness, or any of the symptoms that patients with knee OA typically describe.\(^6\) Given its relative unimportance to OA’s symptomatic presentation, it is ironic that articular cartilage has received so much attention, while other common symptom sources in the knee are ignored. In contrast, the subchondral bone, periosteum, periarticular ligaments, periarticular muscle spasm, synovium, and joint capsule are all richly innervated and are the source of nociception in OA. Interventions that focus exclusively on nourishing, replenishing, or replacing articular cartilage have little chance of providing long-term symptomatic relief unless they also simultaneously relieve strain on other innervated knee structures.

The structural determinants of pain and mechanical dysfunction in OA are not well understood but are believed to involve multiple interactive pathways. Accordingly, OA is best modeled as a disease of organ failure, in which injury to one joint component leads to the damage of other components and collectively to joint failure and the clinical manifestations of OA. The current practice of monitoring only a few features, typically radiographic JSN and osteophytes, therefore, provides only a keyhole view of this disease process and is limited in content validity as an assessment of disease severity. A broader panel of imaging markers, i.e., a whole-organ evaluation, is needed to evaluate properly the structural integrity of joints affected by OA.\(^6\) MRI allows for whole-organ assessment that could help discriminate different patterns of intra-articular involvement in OA.

With respect to clinically important OA, given the poor correlation between the severity of structural damage and the severity of symptoms,\(^7\) it seems the current efforts to develop radiographic protocols that provide maximum sensitivity for detection of JSN,\(^6\) as well as efforts to identify surrogate biomarkers of cartilage breakdown and repair,\(^5,7\) require more focus on structures that are related to symptoms such as synovitis and BMLs. The problem of OA is not structural changes in the cartilage, which almost all of us will develop in time. Rather, the problem is the development of progressive, painful OA.\(^7\) Therefore, the focus of research has been on aneural cartilage rather than on tissues that are likely to be the source of symptoms and those that drive the progression of the disease process, such as BMLs, meniscal pathology, and synovitis.

**Bone Marrow Lesions**

Data has emerged that suggest lesions in the bone marrow play an integral if not pivotal role in the symptoms that emanate from knee OA, and its structural progression.\(^7\) BMLs were found in 272 of 351 (77.5%) persons with painful knees, compared with 15 of 50 (30%) persons with no knee pain (\(p < 0.001\)). Large lesions were present almost exclusively in persons with knee pain (35.9% vs. 2%; \(p < 0.001\)). After adjustment for severity of radiographic disease, effusion, age, and sex, lesions and large lesions remained associated with the occurrence of knee pain. Among persons with knee pain, BMLs were not associated with pain severity. In a more recent analysis using a different semi-quantitative scoring technique, BMLs were associated with pain severity.\(^7\)

An additional study that has identified data on the potency of BMLs as a predictor of progression in knee OA is compelling.\(^7\) Medial BMLs occurred mostly in those with varus and lateral lesions, in those with valgus limbs. Of 75 knees with medial lesions, 25 (36.0%) showed medial progression versus only 12/148 knees (8.1%) without lesions (odds ratio for progression was 6.5, 95% CI, 3.0, 14.0). Sixty-nine percent of knees destined to progress medially had medial lesions. Lateral lesions conferred a similar marked risk of lateral progression. These increased risks were attenuated by 30% to 50% after adjusting for limb alignment. This demonstrates that BMLs are a potent risk factor for structural deterioration in knee OA, and its relation to progression is explained, in part, by its association with limb alignment.

More recently, we demonstrated that BMLs predict cartilage loss measured semi-quantitatively on MRI and characterized the natural history of these lesions.\(^7\) Fifty-seven percent of knees in the BOKS symptomatic knee OA cohort had a BML at baseline, of which 99% remained the same or increased in size at follow-up. Knee compartments with a higher baseline BML score had greater cartilage loss on MRI. Further, an increase in BML size was strongly associated with further worsening of the cartilage score. Enlarging or new BMLs occurred mostly in malaligned limbs on the side of the malalignment (e.g., varus, new medial BML). The association of BML change with medial TF cartilage loss was not significant after adjusting for alignment. Thus, BMLs are unlikely to resolve and often get larger over time. Compared to BMLs that stay the same, enlarging BMLs are strongly associated with more cartilage loss.

**Meniscal Damage and Malposition**

The meniscus has many functions in the knee, including load bearing, shock absorption, stability enhancement, and
lubrication.\textsuperscript{75,76} Knee OA after meniscectomy is traditionally considered a result of the joint injury that led to the meniscectomy in the first instance, as well as the increased cartilage contact stress due to the loss of meniscal tissue.\textsuperscript{77-82} Meniscectomy is often accompanied by the onset of OA, because of the high focal stresses imposed on articular cartilage and subchondral bone subsequent to the excision of the meniscus. The studies that have explored the relationship between the meniscus and risk of disease progression in OA have been small and do not allow precise estimates of risk.\textsuperscript{25,30} Biswal and coworkers\textsuperscript{35} studied 43 subjects and demonstrated a higher average rate of progression of cartilage loss (22%) in 26 subjects who had sustained meniscal tears, compared to those who had intact menisci (14.9%) (p < odds ratio = 0.018). Berthiaume and colleagues\textsuperscript{80} investigated the relation between knee meniscus structural damage and cartilage degradation in 32 subjects and found similar effects. Our study demonstrated a strong association of meniscal position and meniscal damage and cartilage loss.\textsuperscript{8} Each aspect of meniscal abnormality (whether change in position or damage) had a major effect on the risk of cartilage loss.

**Synovitis**

Synovitis is frequently present in OA and may predict other structural changes in OA and correlate with pain and other clinical outcomes.\textsuperscript{8} Quantitative MRI markers of synovitis include the volume of synovial tissue and fluid and the rate of synovial enhancement following intravenous injection of contrast material. It is possible to quantify synovitis semiquantitatively in the absence of Gd-DTPA, and this protocol refers to noncontrast MRI. Synovial thickening around the infra-patellar fat pad using noncontrast MRI has been shown on biopsy to represent mild chronic synovitis.\textsuperscript{83} A semiquantitative measure of synovitis from the infrapatellar fat pad is associated with pain severity and similarly change in synovitis is associated with change in pain severity.\textsuperscript{84}

**Conclusion**

OA is the most common form of arthritis and one of the leading causes of disability in elders. With little currently available in the treatment of this disease, better understanding of the responsive and valid end points is essential to identify potential new interventions for treatment. There are currently a large number of epidemiologic and clinical trials underway in OA that are collecting MRI data. We are still characterizing what the most valid and responsive set of end points is for these studies. Before recommending the widespread use of MRI in structure modifying clinical trials, it is essential that we have this information.

Further, the widespread proliferation of MRI in rheumatology practices has little place for the assessment of OA.\textsuperscript{85} As yet, we do not have agents that can definitively modify structure, and even if we did, the measures currently being used in research to characterize structure are not suitable for clinical use, and will need to be dramatically refined before widespread use is possible.

**Disclosure Statement**

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**


