Osteoarthritis (OA) is no longer viewed as a passive, degenerative disorder, but rather an active disease process driven primarily by mechanical factors. OA should also be conceptualized as a disease of a whole joint organ, and therefore imaging of OA requires techniques which enable us to visualize the whole joint organ. Although clinical decision making based on imaging findings remains controversial the importance of imaging-derived data in OA research cannot be overemphasized. Since mid-2009, numerous publications reporting on imaging-oriented studies on OA have been reported. These include magnetic resonance (MR) imaging of numerous features of the whole joint such as synovitis, subchondral bone, meniscus, cartilage and cyst-like lesions. Active research is also ongoing using conventional radiography with a focus on measurements of joint space width and alignment of the knee joint. Ultrasound is emerging as a useful imaging technique, particularly in the field of hand OA research. As the importance of imaging-derived data increases, all potential authors are advised that they should seek opinions from expert musculoskeletal radiologist to ascertain the application of correct imaging techniques, especially the MR pulse sequences and image interpretation. The peer-review process of OA imaging in any journal, therefore, should involve musculoskeletal radiologists experienced in OA research to ensure the publication of papers with scientifically sound contents.
MR imaging and biomarkers for prediction of disease progression

Research is ongoing to identify factors which potentially predict progression of OA. Today, no disease-modifying OA drugs (DMOADs) are approved by US Food and Drug Administration (FDA). Dam et al. postulated that this might be partly due to inadequate trial design since efficacy demonstration requires disease progression in the placebo group. They showed a combination of biochemical and MRI-based biomarkers improved diagnosis and prognosis of early-stage knee OA and might be useful for selection of high-risk patients for inclusion in DMOAD clinical trials. This study was limited by a use of sparsely-validated 0.18 T magnet. It remains to be seen if similar results can be obtained using a higher-field magnet.

In a cohort study of symptomatic middle-aged women, Davies-Tuck showed the incidence of bone marrow lesions (BMLs) over 2 years was associated with higher levels of total cholesterol and triglycerides. This study was limited by the small number of prevalent BMLs, and a lack of consideration for knee malalignment, which is a factor shown to be associated with incidence and progression of BML.

Berry et al. showed higher bone remodeling is associated with reduced cartilage loss and low levels of cartilage biomarkers at baseline were associated with a significantly reduced rate of medial cartilage volume loss. These studies were limited by not accounting for multiple joint involvement. Further research is needed to determine distinct cut-off points for progression, and larger studies may be needed to assess a combination of biomarkers in further subgroups.

Pelletier et al. showed higher baseline values of interleukin-6, C reactive protein and cartilage oligomeric matrix protein (COMP) were predictive of greater risk of cartilage volume loss. However, over time a reduction in matrix metalloproteinase (MMP)-1 and MMP-3 levels correlated best with reduction in cartilage volume loss and the effect of DMOAD treatment. Limitations of the study include a lack of correction for multiple testing. The findings of this study need to be validated in further studies.

In summary, further research is required to identify what biomarkers, and in which combination, enable us to predict disease progression.

MR imaging of synovitis

Synovitis may be evaluated using non-enhanced or contrast-enhanced MRI. Roemer et al. showed signal alterations in Hoffa’s fat pad on proton density-weighted fat-suppressed sequences were a sensitive but non-specific marker to detect synovitis, compared to evaluation of peripatellar synovial thickening on T1-weighted fat-suppressed contrast-enhanced sequences. Although the study was limited by a lack of histology, it highlighted that contrast-enhanced MRI, which enables differentiation of synovium and effusion, is a better tool for assessing synovitis in OA.

Synovitis is a common phenomenon in OA-affected knees. Roemer et al. semiquantitatively assessed synovitis using contrast-enhanced MRI and showed 89.2% of OA-affected knees exhibited grade ≥2 synovitis. The most common anatomical sites for definite synovitis were posterior to the posterior cruciate ligament and in the suprapatellar region.

Synovitis was shown to have a strong relation with knee pain severity [assessed by Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain scale] by Baker et al. in a study also utilizing contrast-enhanced MRI. In knees with moderate pain, 80% had synovitis. For knee pain, synovitis conferred a 9.2-fold increased odds compared with those without synovitis. A limitation of this, and other contrast-enhanced MRI-based studies, is the lack of reliability data on contrast-enhanced MRI.

Overall, evidence is mounting to suggest optimal characterization of synovitis in OA can be achieved using contrast-enhanced MRI (Fig. 1). For research purposes, contrast administration is essential for accurate assessment of synovitis in OA. This is particularly relevant for the trials in search of effective DMOADs particularly those where the therapeutic target may impact the synovium.

MR imaging of subchondral bone

Pathological features of OA can be found within subchondral bone including bone attrition, BMLs and subchondral cysts. Studies have shown that bone attrition may be a reflection of compartment-specific mechanical load. BMLs lead to incident subchondral cysts in the same subregion of the knee, and BMLs are highly associated with and predict bone attrition longitudinally. Moreover, BMLs were shown to be related to dynamic knee

Fig. 1. Contrast required to accurately assess synovitis. Images from the same knee at the same timepoint with and without contrast. (a) Sagittal non-contrast enhanced proton density-weighted fat-suppressed MRI shows hyperintensity consistent with joint synovial fluid posteriorly (arrowhead) and anteriorly (arrow). (b) Sagittal contrast-enhanced T1-weighted fat-suppressed MRI surprisingly shows homogeneous enhancement around the ACL and PCL (arrows) and also at the suprapatellar region. Thus, what was believed to be joint effusion turned out to be extensive synovitis, and no joint effusion was demonstrated. (Images from the Multicenter Osteoarthritis Study).
loading. The findings of this study support the hypothesis that greater mechanical loading of the medial compartment plays a role in the pathogenesis of BML in medial tibiofemoral OA.

In a phase III clinical trial evaluating the effect of licofelone on knee OA, the presence of, and changes in, BMLs over time was assessed. Unfortunately, this study was flawed because of the use of inappropriate pulse sequences [i.e., 3D spoiled gradient recalled (SPGR) acquisitions with fat suppression, and 3D fast imaging at steady-state precession (FISP) acquisitions with water excitation]. For BML assessments, fluid-sensitive sequences, (i.e., T2-weighted, proton density-weighted or intermediate-weighted spin echo sequence with fat suppression) should be used to delineate the maximum extent of BMLs. Aforementioned gradient-recalled type sequences are not suitable for such purpose (Fig. 2), and consequently it is difficult to derive meaningful conclusions from this study. Another study attempting to evaluate if BMLs predicted progression of knee OA and joint replacement had the same methodological problem.

A prospective study in older adults attempted to describe the association between baseline tibial bone area and tibial subchondral bone mineral density (BMD) with tibial cartilage defect development and cartilage volume loss. The results showed that bone area predicted medial cartilage volume loss, while subchondral BMD did not. It is regrettable to point out that they used gradient-recalled type MR sequences to assess focal cartilage defects, which is an inappropriate methodology because of its proneness to susceptibility artifacts. Fluid-sensitive sequences are more suited to assess focal cartilage defects. Thus, parts of this study (i.e., data dealing with cartilage defects) are thought to be invalid.

OA investigators are advised that the choice of correct MR pulse sequences is critically important, and should seek opinions of expert musculoskeletal radiologists on the choice of pulse sequences.

**MR imaging of meniscus**

Another tissue critical in the etiopathogenesis of OA is the meniscus. Englund et al. showed MRI-detected meniscal pathology increases the risk for both incident and enlarging subchondral BMLs of the knee in the ipsilateral compartment. Over a 30-month period, compartments with medial meniscal pathology had approximately a two-fold increased risk of developing BML than medial compartments without meniscal pathology. Jung et al. demonstrated a high frequency of meniscal hypertrophy in people with advanced varus knee OA. The role of the hypertrophied meniscus in disease progression, its position within the stage of evolution of meniscal morphologic abnormality, and the etiology of hypertrophied meniscus remains to be determined.

Kai et al. showed T2 relaxation values were significantly increased in patients with Grade III meniscal signal-complex tears compared to those without meniscal abnormality over the medial and lateral tibial plateau. Limitations of this study include a lack of arthroscopic and clinical correlation. Nevertheless, these results may have an impact on prognostication and stratification of patients with meniscal tears into different risk categories.

Several authors performed studies using meniscal segmentation techniques. Bowers et al. demonstrated their manual segmentation method showed a significant reduction in the volume of the surgically resected menisci after partial meniscectomy, but no significant change in the volume of unresected meniscal tissue. Wirth et al. presented a technique for 3D and quantitative analysis of meniscal shape, position and signal intensity. The pilot data indicated a greater size, increased meniscal extrusion, and elevated signal intensity of the medial meniscus in OA knees.

**Cartilage morphometry (quantitative MRI)**

Quantitative measurement of cartilage morphology exploits the 3D nature of MRI data sets to assess tissue dimensions (e.g., volume...
and thickness) or signal as continuous variables. Examples of nomenclature for MRI-based cartilage measures include VC (volume of the cartilage), TAB (total area of the bone), AC (area of the cartilage surface), dABp [percentage of TAB not covered by the AC = 100 × (1 – cAB/TAB)], and ThCTAB.Me (mean cartilage thickness over the TAB). As many of these measures are strongly related, some may be redundant or contain minimal additional information. Buck et al. performed a study to identify an efficient subset of core measures that comprises a comprehensive description of cartilage morphology and its longitudinal changes in healthy and disease cartilage. The study showed that three measures (TAB, dABp and ThCTAB.Me) explain nearly all variation in a larger set of common cartilage morphology measures observed in cross-sectional or longitudinal studies, in knees with or without OA. Thus, reporting on this efficient subset of knee cartilage morphology measures is encouraged in future studies.

Another strategy for more efficient measurement of cartilage thickness was proposed by Buck et al. Authors hypothesized that determining the magnitude of thickness change independent of anatomic location provided improved discrimination between healthy subjects and OA participants longitudinally. The study showed that their “ordered values approach” was sensitive in detecting cartilage thickness changes. This novel method may potentially become a useful tool in DMOAD trials.

Ding et al. examined the associations between non-steroidal anti-inflammatory drugs (NSAIDs) and changes in knee cartilage volume. Comparing users of cyclooxygenase (COX)-2 inhibitors with users of conventional NSAIDs, the latter had higher knee cartilage volume loss. In another clinical study, Raynauld et al. evaluated the effect of celecoxib on cartilage volume loss over 12 months in knee OA. However, it did not provide a protective effect on knee cartilage loss.

**MR imaging of peri- and intra-articular cyst-like lesions**

Peri- and intra-articular cyst-like lesions are features which are generally thought to be a secondary phenomenon commonly seen in OA-affected knee, rather than the cause of OA. Two papers were published and their findings confirmed our understanding mentioned above. None of the cyst-like lesions seemed to be a marker of radiographic OA severity in painful knees, or an independent predictor of incident knee pain or radiographic OA longitudinally.

**Estimation of articular contact stress using MRI**

Segal et al. demonstrated the maximum articular contact stress was higher in incident OA cases compared to that in control knees. The findings suggest a biomechanical mechanism for incident tibiofemoral OA and support the ability to identify risk by subject-specific biomechanical modeling. One of the limitations of this study was the lack of incorporation of the meniscus, which might have influenced estimates of contact stress. Further model development may benefit from addressing the menisci and variations in cartilage thickness.

**Plain radiography-based studies of knee OA**

In a prospective observational cohort study by Harvey et al., leg-length inequality of ≥1 cm was associated with prevalent radiographic and symptomatic OA in the shorter leg, incident symptomatic OA in the shorter and longer legs, and increased odds of progressive OA in the shorter leg over 30 months. The study was limited by the small number of incident radiographic OA cases. However, these results point to leg-length inequality as a potentially modifiable risk factor for knee OA.

Duryea et al. compared the responsiveness of radiographic joint space width using automated software with MRI-derived measures of cartilage morphometry for OA progression. Results demonstrated that new measures using a software analysis of digital knee radiographic images were comparable with MRI in detecting OA progression. Although limitations of radiography are well known, considering the cost-effectiveness of radiography compared with MRI, this study showed that the radiography still has potential roles to play in OA trials.

In a clinical trial of the effect of doxycycline on medial joint space narrowing, Mazzucca et al. showed varus malalignment negated the slowing of structural progression of medial-compartment OA by the drug. It remains to be seen if the same effect can be obtained on MRI-based evaluation of OA progression.

**Ultrasound-based study of the knee OA**

Chao et al. assessed whether inflammation on ultrasound is predictive of clinical response to intra-articular corticosteroid injections in patients with knee OA. Somewhat counterintuitively there was a significantly greater improvement in WOMAC pain scores among non-inflammatory patients than among inflammatory patients at 12 weeks. The study was performed on a small patient subset, and imaging was limited to suprapatellar pouch, which might have decreased the sensitivity for detecting synovitis in the knee. Also, addition of Power Doppler imaging might have increased the specificity for detecting active synovial inflammation. Assessments of response to steroid injections are clinically relevant, and usefulness of ultrasound in knee OA research needs to be further evaluated.

**Imaging of patellofemoral OA**

Publications on patellofemoral OA are less common than those on tibiofemoral OA, but research efforts are ongoing. In an MRI-based study, Crossley et al. demonstrated patellar tape resulted in a significant lessening of lateral alignment, with reduced lateral displacement and increased lateral patellar tilt angle. In a longitudinal study using quantitative MRI, Teichtahl et al. showed participation in vigorous physical activity at baseline was associated with a reduced annual rate of patella cartilage volume loss. Moreover, using data from Osteoarthritis Initiative (OAI), Stehling et al. demonstrated a significant correlation between patellar cartilage T2 values and the severity and grade of cartilage and meniscal lesions. Subjects with high activity levels had significantly higher prevalence and grade of abnormalities and higher T2 values. Additional studies are awaited to determine the causality of these phenomena. Lastly, Yao et al. demonstrated T1 and T2 relaxation times were relatively sensitive to early degenerative changes in the patellar cartilage, using the delayed Gadolinium-Enhanced MRI (dGEMRIC) and T2 mapping techniques. These measures seemed to be a better biomarker than magnetization transfer ratios with regard to early detection of OA. These findings, however, are confirmatory. Interestingly, authors also showed a negative correlation between T1 and T2 relaxation times as a novel finding. Further studies are needed to assess the interrelationships among various quantitative measures including T2, T1 (1/rho) and dGEMRIC index.

**Imaging of hip OA**

Hip is another large joint commonly affected by OA. In a large prospective cohort study, Javaid et al. demonstrated that a wider femoral neck and more medial centroid position of bone mineral in the femoral neck and more medial centroid position of bone mineral in the femoral neck and more medial centroid position of bone mineral in
the femoral neck were associated with an increased risk of prevalent, incident, and progressive radiographic hip OA, independent of areal BMD. McWilliams et al. performed a case-control study to determine if mild variation in acetabular depth and shape is a risk factor for hip OA. Results suggested constitutional mild acetabular dysplasia (which affects acetabular depth and center edge angle) appeared to increase the risk of hip OA. Gosvig et al. studied the prevalence of anatomical malformations of the hip joint in a Danish community (Copenhagen Osteoarthritis Substudy cohort). A deep acetabular socket and a pistol grip deformity were common radiographic findings and were associated with an increased risk of hip OA. Their findings suggested an increased focus on early identification of malformation should be considered. Finally, Jessel et al. showed significant correlations between dGEMRIC index, pain and alpha angle in OA-affected hips with femoroacetabular impingement. Hips with more femoral deformity showed signs of early OA. This study demonstrated dGEMRIC might be a useful technique for diagnosis and staging of early hip OA with impingement.

Imaging of hand OA

Active research efforts are also ongoing in the field of hand OA. Bijsterbosch et al. demonstrated, in symptomatic hand OA, carpo- metacarpal joint OA contributes more to pain and disability than interphalangeal joint OA. Paradowski et al. showed, in subjects with prior meniscectomy, OA of distal interphalangeal, first carpo- metacarpal and first interphalangeal joints are common. However, further hand OA progression over 10 years, as detected by radiography, was relatively modest. More sensitive imaging techniques might be needed for clinical trials to evaluate structural hand OA progression.

Ultrasound enables visualization of effusion, synovitis, erosion and osteophytes in OA-affected hand joints. Kourtroumpas et al. demonstrated ultrasound detected more joints with inflammation than clinical examination in patients with erosive OA. Wittoek et al. showed the presence of the highest frequency of synovitis in erosive OA joints, but inflammatory findings were common in both erosive and non-erosive OA. Mancarella et al. demonstrated ultrasound-detected synovitis is present in about 10% of OA-affected finger joints and was associated with more severe radiological damage and reduced cartilage thickness. Moreover, gray-scale synovitis, effusion, synovial thickening and Power Doppler signals were shown to be associated with pain in hand OA by Koertekaas et al. Finally, Keen et al. found parenteral corticosteroids were associated with a statistically significant reduction in symptoms but not in ultrasound-detected synovial inflammation. The latter findings may reflect the relatively low levels of synovial inflammation detected by ultrasound. Ultrasound seems to be an informative tool for hand OA evaluation and its use is becoming increasingly common in hand OA research. This trend is expected to increase further.

Conclusion

Numerous reports utilizing various imaging techniques were published over the course of the past year. Some major advances in our scientific understanding include the importance of contrast-enhanced MRI for evaluation of synovitis in OA. Additionally, use of ultrasound for imaging of OA-affected joints is becoming increasingly common. Thus, future research efforts in imaging of OA are likely to shift further from conventional radiography-based studies to those directly visualizing the target tissues including modalities utilizing semiquantitative or quantitative MRI and ultrasound. Application of contrast-enhanced MR imaging should be encouraged where appropriate to adequately visualize synovitis. The importance of biomechanics in disease progression needs to be recognized with adequate visualization of joint tissues under physiologic loading conditions. Finally, despite rigorous peer-review process before publication of articles, we are still seeing a number of reports with fundamental methodological shortcomings, particularly concerning the choice of MR pulse sequences. Thus, involvement of an expert musculoskeletal radiologist in the early phase of study design and in the peer-review process should be strongly encouraged for papers dealing with OA imaging-derived data.

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References


25. Kai B, Mann SA, King C, Forster BB. Integrity of articular cartilage on T2 mapping associated with meniscal signal change. Eur J Radiol 2010 [Epub ahead of print].


