Imaging of knee osteoarthritis: data beyond the beauty
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Purpose of review
MRI has revolutionized osteoarthritis research by providing semi-quantitative and quantitative imaging endpoints on most articular tissues. With the first image data of the Osteoarthritis Initiative now becoming publicly available, this article reviews recent developments in quantitative imaging of osteoarthritis.

Recent findings
Although radiography remains the standard for regulatory studies on disease modifying osteoarthritis drugs, there is no consensus on the optimal positioning and acquisition protocol. With MRI, semi-quantitative scoring systems for evaluation of multiple articular tissue changes have been developed and are currently investigated in the context of correlation with symptoms and of predicting structural progression of osteoarthritis. Most efforts on quantitative measurement of imaging endpoints have focused on cartilage morphology and composition, with higher field strength (3T), newer sequences, and new measurement endpoints being a driver of current innovation.

Summary
The semi-quantitative and quantitative tools for analysis of articular structure are now available and permit comprehensive analysis of morphological and compositional tissue changes in osteoarthritis. These changes will need to be related to clinical outcomes (e.g. how a patient feels or functions) with current epidemiological studies, such as the Osteoarthritis Initiative, providing the opportunity for clinical validation of these imaging biomarkers.

Keywords
clinical outcome, diarthrodial joint, MRI, osteoarthritis

Introduction
MRI has made a fundamental impact on osteoarthritis research by providing the opportunity to determine semiquantitative or quantitative imaging endpoints of most articular tissues. This is of particular interest for characterizing the risk factors for osteoarthritis in epidemiological studies and for the evaluation of disease (structure) modifying therapy (disease-modifying osteoarthritis drugs; DMOADs) efficacy in osteoarthritis, which has so far not been approved by regulatory agencies. With the first imaging data of the Osteoarthritis Initiative (OAI; website: http://www.niams.nih.gov/ne/oi/) now becoming publicly available, this article reviews recent developments in quantitative imaging of osteoarthritis, including radiography, semi-quantitative scoring of magnetic resonance (MR) images, and quantitative measurement of articular cartilage morphology and composition in osteoarthritis.

Radiography
Radiography is the technique currently accepted by regulatory agencies for evaluating DMOADs, but currently no consensus exists on the optimal positioning and acquisition protocol [1–3,4,5]. Radiography is limited by projectional errors [5,6], and joint space narrowing (JSN) is influenced not only by cartilage, but also by meniscal status [7,8,9]. Le Graverand et al. [5] reported that in 80 persons with knee osteoarthritis near-parallel alignment of the tibial plateau was achieved more frequently with a fluoroscopically guided semi-flexed anterior–posterior protocol than with a nonfluoroscopic fixed flexion or metatarso-phalangeal (MTP) protocol. Paired radiographs with near-parallel alignment showed more rapid and less variable JSN than the total cohort. In another comparative study [4], fluoroscopic guided radiography showed a greater magnitude and lower standard deviation of JSN (0.42 mm) than fixed
flexion (0.63 mm) or MTP (0.53 mm). There was, however, insufficient power to control for differences in study durations and inclusion criteria. With this level of imprecision and lack of ability to exclusively monitor one target tissue, radiography has inherent limitations in epidemiological and DMOAD studies.

**Semi-quantitative scoring of MRI**

Traditionally, osteoarthritis has been considered a disease of articular cartilage. During a US National Institutes of Health workshop, ‘Consensus on osteoarthritis imaging’ in Bethesda [10], experts still ranked articular cartilage to be the most important MRI feature of osteoarthritis severity and progression, but osteophytes, bone marrow lesions (BMLs), synovitis, meniscal abnormality and synovial effusion were also considered important [10]. The current concept holds that osteoarthritis involves the entire joint organ (Fig. 1) [11].

Semi-quantitative scoring of the knee relies on an observer to score a variety of features believed to be relevant to the functional integrity of the joint or potentially involved in the pathophysiology of osteoarthritis. A number of semi-quantitative whole-organ scoring methods have been developed and tested [12–15]. MR sequences for semi-quantitative scoring vary depending on the target tissue of interest, scanner type, and investigator preference, but the Bethesda NIH imaging workshop [16] and the imaging working group of the OAI have recently made recommendations on sequences that will capture most of the information for scoring tissue in the whole knee in osteoarthritis (website: http://www.oai.ucsf.edu/datarelease/About.asp).

The importance of using validated observers and instruments was highlighted by a study [17] that reported an accuracy of only 52% for medial meniscus and of 77% for cartilage lesions, when rated by independent imaging institutions rather than musculoskeletal MRI specialists; 37% of the operations supported by MRI were reported as unjustified [17]. Conaghan et al. [18] evaluated the internal construct validity of the semi-quantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS) [12] in two osteoarthritis cohorts by applying a Rasch model. Because few of the subscales met the

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**Figure 1**

The images were obtained from the Osteoarthritis Initiative (OAI) database, which is available for public access at http://www.oai.ucsf.edu. The specific datasets used are from image release GB1 and 1B1. (a) Axial image depicting moderate effusion, medial and lateral patella and posterior femoral osteophytes, full thickness cartilage loss and cysts in the lateral trochlea. (b) Coronal double echo steady state (DESS) image depicting full thickness cartilage loss on the medial tibia and femur, osteophytes and the macerated remnants of medial meniscus. (c) Sagittal fat suppressed image depicting full thickness cartilage loss in central weight bearing portions of the tibia and femur and bone marrow lesions in the medial femur and tibia, and moderate sized effusion.
requirements of the model, constructing outcome measurements that sum different features of complex pathological structural change throughout several anatomical sites is problematic [18*]. These studies have prompted the re-evaluation of current scoring schemes and development of novel scoring methods.

Recent applications of semi-quantitative scores have started to cast light on symptom etiology and disease etiopathogenesis of osteoarthritis. Earlier studies reported that all [19] or larger BMLs are associated with pain [20], but other studies have failed to show such relationships [21]. Kornaat et al. [22**] recently reported that synovial effusion and patellofemoral osteophytes, but not cartilage abnormalities, BMLs, or other structural changes were related to pain. Another study found knee pain severity to be associated with subarticular bone attrition, BMLs, synovitis/effusion, and meniscal tears [23**], when using WORMS for the worst compartment. The contribution of BMLs to pain severity appeared to require the presence of bone attrition [23**].

Meniscal position was found to be correlated with meniscus damage [24*] and both were identified to predict progression of cartilage lesions in MRI. BMLs were found to infrequently regress [25*] and an increase in their size was correlated with cartilage loss. BML location and change in size was mediated by alignment [25*]. Further work with standardized and valid measures in larger samples will be required to elucidate which of these structural abnormalities are associated with current or prospective symptoms or subsequent cartilage loss.

One study evaluated the responsiveness of whole organ scoring (WORMS) [12] and cartilage volume change in 150 subjects with knee osteoarthritis from a randomized, double-blind trial at baseline and 6-month follow-up [26**]. Of all features measured, cartilage morphology, synovitis and osteophytes appeared to be the most responsive, but the effect size and smallest detectable differences were found to be very small.

**Quantitative measurement of articular cartilage morphology with MRI**

Because structural changes in osteoarthritis may be very subtle and slow, quantitative measurement of articular structures throughout contiguous MR images may reveal changes that are not apparent during scoring. Amongst joint tissues, articular cartilage has received most of the attention (Fig. 2). Water-excitation T1-weighted spoiled gradient echo (SPGR) imaging at 1.5 T represents the current gold standard sequence for quantitative measurement of cartilage morphology [16*,27,28*], but more efficient sequences [29] and imaging systems (up to 7 T [30*]) have recently become available. Three Tesla cartilage imaging has been validated and shown to reduce precision errors compared with 1.5 T [31,32**]; results from different vendors have shown to be comparable at 3 T [33]. Peripheral 1.0 T scanners have also been cross-calibrated versus 1.5 T cartilage measurement [34], as these potentially permit more widespread application of this technology. Precision errors, however, were found to be somewhat higher than at 1.5 T [34].

Most investigations on cartilage morphology have focused on cartilage volume (changes), but this has inherent limitations as an outcome measure. Subjects with larger bones display larger cartilage volume, limiting the ability to discriminate between osteoarthritis patients and normals [35]. Women have smaller joint surfaces than men (and hence also cartilage volume), even after adjustment for body height and weight [36]. In longitudinal studies, the subchondral bone area increases by about 1% with normal aging, consistent with theories of metaphyseal expansion [37]. Such effects may mask longitudinal reduction in cartilage thickness, if only cartilage volume is measured. To provide a uniform nomenclature in scientific communications, an international group of experts has proposed how morphological and composition parameters of cartilage should be named and defined, and which minimal methodological information should be described [38**].

The OA (website: http://www.niams.nih.gov/ne/oi/) is a 4-year observational study in over 4000 patients, targeted at identifying the most reliable and sensitive biomarkers for evaluating the development and progression of symptomatic knee osteoarthritis. The first results from OA pilot studies have been published. One study has compared near-isotropic, sagittal double echo steady state (DESS) [39], a sequence with greater T2-weighting, with previously validated coronal SPGR [32**]. The DESS displayed similar test–retest precision of femorotibial cartilage morphology, but precision errors in the femoropatellar joint were higher than those previously published for sagittal SPGR [40]. Another study [41*] reported that, despite the higher signal-to-noise ratio of the cartilage achieved with phase array coils, these did not translate into lower precision errors compared with quadrature knee coil measurements.

Reports on longitudinal changes of cartilage morphology [28*,42–44,45**,46,47,48**,49**,50*] have varied substantially between studies (0–7% annually). A meta-analysis of available data reported annual changes of 4–6% in most knee compartments [28*]. Estimates of annual cartilage loss over 2 years were found consistent with those over 4.5 years in the same cohort, indicating that 2-year change predicts long-term cartilage loss [45**]. Medial tibial cartilage loss was associated with lesser severity of baseline knee pain, but was independent of age, BMI and other factors [45**]. Raynauld et al.
reported cartilage volume changes in 107 patients with knee osteoarthritis to be \(-5.5 \pm 4.3\%\) in the medial compartment at 12 months, and \(-8.3 \pm 6.5\%\) at 24 months. The rate of change was associated with meniscal extrusion and tears, bone marrow edema and high BMI. No association was found with JSN (radiographs) or urine biomarker levels [48**]. Other studies also found only weak correlations between MRI and radiographic change [46,50*,51].

When evaluating the effects of misalignment, relatively small changes in cartilage thickness (<1.5% per annum) were found in subjects with a neutral knee axis [52]. Higher rates of change were reported in the medial knee compartment with varus \((-3.1 \pm 4.0\%)\), and in the lateral knee compartment with valgus malalignment \((-2.9 \pm 4.3\%)\), whereas opposite compartments displayed no significant change, respectively. In a nonosteoarthritic cohort, in contrast, baseline knee alignment was not
associated with subsequent cartilage volume loss or progression of chondral defects [53]. Approaches for determining subregional cartilage thickness have shown promise for more sensitive detection of structural change than analysis of entire cartilage plates [54–56].

Studies on how cartilage loss relates to symptoms have produced contradictory results [46,55,57–59]. One study, however, reported that the rate of cartilage loss over 2 years was associated with a clinical endpoint (risk of receiving knee arthroplasty 2 years later) [60]. The OAI and other large trials will soon make it possible to relate longitudinal changes of cartilage to clinical outcome.

Quantitative measurement of articular cartilage composition with MRI

While quantitative measurement of morphology can be used to monitor loss of cartilage tissue, there is also great 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 [49**,61–64].

For research applications, the quantitative measurement of the cartilage transverse relaxation time (T2) provides a potential imaging biomarker to identify and monitor structural changes in the collagen matrix (Fig. 3) [65]. Perturbation of the collagen architecture leads to increased T2-weighted signal intensity; however, sites of decreased signal intensity can be observed adjacent to sites of focal cartilage injury [66]. The majority of cartilage T2 mapping studies used conventional multislice multi spin echo (MSME) sequences, typically with a minimum of seven echoes. Although fewer echoes have been used, there is theoretical concern that T2 measurements obtained using only two echoes are prone to large error due to under sampling of the T2 decay curve, artifact from stimulated echoes, and error due to variability in image signal to noise. Using a 1.5 T magnet and turbo spin echo (TSE) MSME sequence with eight echoes, the precision error was 3–7% and 6–29% for global and regional patellar cartilage T2, respectively [67*]. While potentially more efficient in measuring T2, these TSE or fast spin echo techniques have not yet been validated.

While increased cartilage T2 is associated with an increase in water content [68] and a decrease in collagen content [69], the dominant factor influencing regional variation in T2 is the anisotropic arrangement of the type II collagen matrix [70,71]. There is a strong inverse correlation of fiber anisotropy determined with polarized light microscopy and cartilage T2 [72]. This sensitivity to collagen architecture has been used to identify maturational changes in the collagen matrix of osteochondral plugs from juvenile animals [73*,74]. A recent study of asymptomatic humans confirmed an age dependent increase in T2 in adult cartilage [75]. Prior studies using depth resolved cartilage T2 mapping demonstrated an age-dependent elevation in T2, initially near the articular surface, and progressing to deeper layer with increasing age [76,77]. These studies have indicated that cartilage T2 mapping provides a noninvasive endpoint that is sensitive to developmental and senescent changes in the collagen matrix that could be useful for future studies on human cartilage development and aging. Initial results in osteoarthritis were mixed, with some studies observing discrete differences of T2 between control and osteoarthritis populations [78,79] whereas others did not [80,81].

The delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique relies on preferential distribution of the MRI contrast agent GdDTPA\(^{2-}\) into cartilage with low glycosaminoglycan content [82,83]. To adjust for differences in biodistribution of GdDTPA\(^{2-}\), the dose should be adjusted for BMI [84]. Although initial dGEMRIC techniques were limited to single slice acquisition, rapid three-dimensional applications of dGEMRIC that provide greater coverage and faster imaging times are currently undergoing validation [85,86]. Preliminary clinical applications of dGEMRIC for identification of early cartilage damage in the hip [87,88] have been promising. In a recent prospective study, low dGEMRIC scores indicative of low cartilage glycosaminoglycan (GAG) content were predictive of poor outcome in periacetabular osteoplasties for hip dysplasia [89**].
Using a combination of T2 mapping and dGEMRIC parameters, it is possible to estimate biomechanical properties of cartilage tissue [90], which may provide insight for guiding cartilage repair [91]. Both cartilage T2 mapping and dGEMRIC have been used for evaluation of reparative tissue following surgical repair of focal cartilage defects [92–94]. Longer heterogeneous T2 values were observed in repair tissue following autologous chondrocyte implantation (ACI) [95**]. The dGEMRIC scores in repair tissue were similar to those observed in normal cartilage, suggesting replenishment of GAG 10–15 months after ACI [95**]. Following arthroscopic osteochondral autograft transplantation (OAT), the normal decrease in cartilage T2 with respect to depth from the articular surface was predictive of hyaline cartilage histology, while heterogeneous T2 values were indicative of fibrocartilage repair tissue [96**]. Additional studies are needed to determine if parametric mapping techniques are prognostic of clinical outcome, or could replace arthroscopic biopsy for monitoring repair tissue histology.

T1rho is another emerging technique for evaluating GAG [97], but has also been shown to be sensitive to collagen [69]. Recent development of a rapid three-dimensional T1rho technique has been demonstrated in proof of concept studies [98*,99]. Although less widely available than T2 mapping studies, initial evaluation in a small number of subjects suggest it may be more responsive to cartilage damage associated with osteoarthritis [79,100*].

**Conclusion**

MRI holds considerable promise to become an invaluable tool in osteoarthritis epidemiology research and the development of structure modifying therapy. Sequences for ‘whole organ assessment’ and quantitative measurement of cartilage morphology are readily available on state-of-the-art 1.5 T and 3.0 T clinical scanners and have been validated. Quantitative data on cartilage composition are emerging and hold promise to detect osteoarthritis changes early. An important question to address is the relationship of these new imaging biomarkers with clinical endpoints and whether use of DMOADs has potential clinical benefits. Therefore, future research must focus on the question of whether structural (imaging) changes represent valid surrogate markers of clinical outcomes several years later. Ongoing initiatives in enhancing measurement methods and the availability of richer data resources should facilitate rapid advances in our understanding of this pervasive condition in coming years and to develop effective disease modifying therapy.

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

**Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 511–512).**


This was one of the few studies comparing different radiographic protocols, but was limited by the fact that technical characteristics such as image receptor and nonfluoroscopic guided radiography, however, showed a greater magnitude and lower standard deviation of joint space narrowing (higher standardized response mean) than nonfluoroscopic techniques (fixed flexion or metatarsal-phalangeal).


This study reported that paired radiographs with near-parallel alignment showed a higher standardized response mean for joint space narrowing than those without, and that near-parallel alignment of the tibial plateau was achieved more frequently with the fluoroscopically guided semi-flexed anterior–posterior protocol than with the nonfluoroscopic fixed flexion or metatarsal-phalangeal protocol.


This study highlighted that the meniscus (both its position and degeneration) accounts for a substantial proportion of the variance in joint space width, and that the change in meniscal position accounts for a substantial proportion of change in JSN. This has important implications for trials testing osteoarthritis disease modifying treatments.


This review provides a comprehensive summary on current MRI methods for identifying and quantifying noncartilaginous structures and summarizes their associations with both osteoarthritis symptoms and structural progression of osteoarthritis.


This study summarized MRI protocol and sequence considerations for whole organ assessment in osteoarthritis.
This study highlighted that MRI assessment of joint integrity has only limited findings, including focal or diffuse cartilaginous abnormalities, subchondral cysts, bone marrow edema, subluxation of the meniscus, meniscal tears, or Baker cysts, were not associated with symptoms.

This study in 143 patients with primary (idopathic) knee osteoarthritis and definite Tibiofemoral osteophytes reports a significant increase in median pain for bone attrition, bone marrow lesions, meniscal tears, and grade 2 or 3 synovitis/effusion, borderline significance for osteophytes and cartilage status, and no significance for bone cysts or meniscal subluxation.

This study described cartilage volume loss in a cohort 78 subjects over a period of 25 and 4.5 years, respectively. The annual percentage losses (over 4.5 years) were 4.7% (mean ± SD) in the medial tibia and 4.4 ± 4.7% (mean ± SD) in the medial tibia and 4.4 ± 4.7% (mean ± SD) in the lateral tibia. Cartilage volume in each individual seemed to track over the study period relative to other study participants.

This study in 217 subjects highlighted that bone marrow lesions are unlikely to resolve and often get larger over time. Compared to BME that stay the same, enlarging BMLs are strongly associated with more rapid cartilage loss. Further-more, change in BML is mediated by limb alignment.

This study in 150 subjects identified that MRI measures of cartilage morphology, synovitis and osteophytes appeared to be more responsive to change than other measures, albeit all the effect sizes and standardized response means were small.

This study described cartilage volume loss in a cohort 78 subjects over a period of 2 and 4.5 years, respectively. The annual percentage losses (over 4.5 years) were 3.7 ± 4.7% (mean ± SD) in the medial tibia and 4.4 ± 4.4% in the lateral tibia. Cartilage volume in each individual seemed to track over the study period relative to other study participants.

This is the first study from the Osteoarthritis Initiative (OAI) pilot study and compares the test–retest precision of a double echo steady state magnetic resonance imaging of knee articular cartilage at 3 Tesla: a pilot study for the Osteoarthritis Initiative. Ann Rheum Dis 2006; 65:433–441.

This proposal by an international group of experts presents a nomenclature for definitions and names to be used in scientific communications on MRI measurement of cartilage morphology or composition and gives recommendations as to which minimal methodological information should be provided when reporting MRI-based measures of articular cartilage in osteoarthritis.

This study was the first to apply phase array coils in quantitative cartilage imaging, derived from Osteoarthritis Initiative pilot data. The study reported no increased precision of cartilage morphology with phased array coils, despite higher contrast-to-noise ratios for cartilage tissue.

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This review provides a comprehensive summary on current methodology for quantitatively, and its association with symptoms, radiographic change, and risk factors of osteoarthritis. This study has described cartilage volume loss over 12 and 24 months, respectively, and its association with symptoms, radiographic change, and risk factors of osteoarthritis. This study reports on 47 patients undergoing a Bernese periacetabular osteotomy. Nojiri T, Watanabe N, Namura T, Tiderius C, Hori M, Williams A, Boesen M, Jensen KE, Qvistgaard E, Lifetime evaluation of delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage delineation after intra-articular than intravenous gadolinium injection. Magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage delineation after intra-articular than intravenous gadolinium injection. dGEMRIC protocol issues for delayed gadolinium-enhanced MRI of cartilage. Osteoarthritis Cartilage 2006; 14:1265–1271. This study demonstrated sensitivity of cartilage T2 mapping to developmental changes in the collagen matrix. Shinar H, Navon G, Multinuclear NMR and microscopic MRI studies of the articular cartilage nanostructure. NMR Biomed 2006; 19:877–893.


Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2—preliminary findings at 3 T. Radiology 2000; 214:259–266.


This was one of the first studies comparing biomechanical properties of cartilage repair tissue following autologous chondrocyte implantation with dGEMRIC scores and T2 mapping. Combining these two quantitative magnetic resonance imaging techniques enables a more comprehensive characterization of cartilage repair than using dGEMRIC values alone [91].


In this study, cartilage T2 mapping was performed on 10 equines knees that had undergone osteochondral autograft transplantation (OAT) and microfracture arthroplasty (MFX) 12–24 months prior to the MRI. The spatial distribution of cartilage T2 and subjective assessment of cartilage T2 spatial distribution was compared with histologic results and collagen organization assessed at polarized light microscopy. A normal spatial variation in cartilage T2 was correlated with hyaline cartilage in OAT graft sites, while heterogeneously elevated T2 was observed in microfracture and OAT harvest sites demonstrating fibrous repair tissue. The study is important because it provides evidence that T2 mapping is sensitive to repair tissue histology and may have the potential to differentiate hyaline from fibrocartilage repair tissue.


This technical paper describes modifications of a 3D gradient echo T1rho mapping technique at 3T that leads to decreased acquisition time and lower specific absorption rate.


This is an interesting preliminary study of osteochondral tissue samples from eight subjects undergoing total knee replacement and reports elevated T2 and T1rho values in osteoarthritic cartilage compared to healthy tissue. Compared to T2, T1rho demonstrated a larger dynamic range suggesting it may be more responsive than T2 to cartilage degradation.