8. Quantitative magnetic resonance imaging in the evaluation of structural changes in knee osteoarthritis patients

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Abstract. The quantitative evaluation of knee osteoarthritis (OA) cartilage damage and other joint structural changes and their progression over time has become a reality with the use of magnetic resonance imaging (MRI). Although anatomical changes could be seen by this and other radiological means, quantification of the cartilage alterations has been a real challenge for many years. Quantitative MRI (qMRI) assessment of cartilage volume/thickness with fat-suppressed gradient echo sequences and digital post-processing techniques offers high accuracy and adequate precision for studies in OA patients, and robust acquisition protocols for multicentre trials are now available. qMRI provides reliable data on cartilage volume throughout all the compartments and topographical areas of the knee in addition to relevant information on other knee tissue structures. By using MRI, studies have revealed strong correlations between cartilage volume loss and meniscal damage and subchondral bone edema, which are
now considered important risk factors for OA progression in addition to some clinical factors. These advances in MRI technology have enabled the evaluation of knee joint damage and OA progression over time in both cross-sectional and longitudinal studies. Moreover, qMRI can now be used in human clinical trials to evaluate treatment response to disease modifying OA drugs. Therefore, using qMRI as a tool in OA trials offers the further benefits of substantial reduction in number of patients needed for a study and reduced overall study length resulting in improvement of patient retention, compared to using standardized radiographs. Of great interest, there is now fully automated qMRI assessment for some of the knee OA structures including cartilage volume, osteophytes and synovial effusion.

**Introduction**

Assessment of structural damage of the articular cartilage is important for monitoring the progression of osteoarthritis (OA) and evaluating therapeutic response. For many years, clinical studies of drug interventions on symptomatic knee OA have focused mainly on clinical parameters such as pain and joint function, using self-administered questionnaires, but without assessing the effect of treatment on joint structural changes caused by the disease or the role of treatment in preventing cartilage degradation. However, although attempts have been made to evaluate cartilage damage and its progression in OA using radiographs or arthroscopy, these means showed major limitations.

Firstly, serial radiographs of affected joints were used for documenting the progression of OA over time [1] but the sensitivity to changes in the articular structure needed improvements in the standardization and interpretation of radiographs. Although such improvements have produced good measurements of joint space width (JSW) and the progression of joint space narrowing (JSN) [2, 3], the sensitivity to change requires a minimum follow-up of 2 to 3 years and a large number of patients (at least 1,500 for a two-arm study) in order to establish the effect of a pharmacological intervention on OA progression. Moreover, JSW is dependent on the integrity of the surrounding tissues, especially the meniscus and the subchondral bone, preventing it from acquiring information solely on the cartilage changes. For example, enucleation of the medial meniscus of the knee, which may occur during longitudinal studies, can significantly affect the JSW value and this measurement’s reliability [4]. In turn, this could also impair its use in the assessment of cartilage degradation over time. Furthermore, JSN progression provides only one measurement point, which considerably restricts the statistical power of this technique, in addition to giving no indication of the cartilage volume but only a measurement of the space between the condyle
and the tibia bones. The other means, arthroscopy, although shown to reliably and sensitively assess cartilage changes at one year [5], enables only the cartilage surface to be evaluated. This method is also semi-quantitative and, above all, invasive. Large studies using this tool are, therefore, difficult to conduct.

Magnetic resonance imaging (MRI) allows precise visualization and assessment of joint structures such as cartilage, bone, synovium, ligaments and menisci and their pathological changes. MRI acquisitions are non-invasive and non-radiant, providing a clear advantage over arthroscopy and fluoroscopy.

Clinical practice for MRI acquisition of the knee

The use of a 1.5 Tesla (T) or 3.0 T magnet is nowadays mandatory for quantitative evaluation of cartilage volume. The MRI acquisition of the knee is performed with a knee coil, also called an extremity coil because most are compatible with ankle acquisition. This coil entirely surrounds the knee, providing a more homogeneous signal and better image quality (Figure 1).

![Figure 1](image.png)

**Figure 1.** Human knee cartilage in sagittal view acquired with a 1.5 Tesla magnet using a fast imaging at steady state precession (FISP) acquisition with fat suppression. This acquisition sequence produces maps with the highest cartilage contrast. Cartilage interfaces are delineated.
The patient lies on the table in supine position and is inserted feet first in the magnet. The coil is not centered in the magnet but is shifted to the side of the pathologic knee for better patient comfort. Sagittal slices of about 1-1.5 mm are at present used for cartilage volume quantification. Throughout any longitudinal study, the field of view is constant to preserve the pixel resolution and is fixed between 140-160 mm. To allow the best quality, a 512×512 matrix is used for a final 0.3125×0.3125 image resolution [6]. A fast-imaging acquisition technique preserving short repetition time is also used to ensure an acceptable acquisition time. If the protocol is correctly set up, the main cause of artefact is the movement of the patient, which can result in the sequence being rejected during quality control assessment. Proper immobilization of the knee in the coil is a major key to prevention of patient movement.

Advances in MRI technology have led to significant improvement in spatial resolution and contrast, enabling researchers to evaluate anatomical damage of all the joint structures across both cross-sectional and longitudinal planes. For cartilage volumetry, gradient echo sequences are preferred to spin echo and are configured in T1 weighted acquisitions. The most commonly used gradient echo sequences are the FLASH (fast low angle shot), spoiled GRASS (gradient recalled acquisition at steady state), SPGR (spoiled gradient recalled), FISP (fast imaging at steady state precession), or DESS (double echo at steady state). Moreover, 3D sequences are preferred to 2D sequences for the spatial continuity of the signal providing better coherence between the slices and reducing variability at reading time. To reduce partial volume artefact due to the shape of the joint, sagittal acquisitions are most commonly used when cartilage volumetry is performed on the global knee. However, for studies focusing only on the tibiofemoral portion of the joint (excluding the posterior condyle), coronal acquisitions are suitable. Additionally, fat suppression is required to provide a sufficient dynamic range to the image contrast to delineate the cartilage, but also to eliminate chemical-shift artefacts, which arise at the cartilage-bone interface. This is accomplished either by spectral fat-saturation (FS) using a prepulse tuned to the resonant frequency of fat or by frequency selective water excitation (WE). Acquisition times are generally shorter for selective WE protocols than for those using FS, as the latter requires an additional pulse at the beginning of the sequence.

**Knee cartilage volume quantification**

Although structural cartilage changes can be seen with the above acquisitions, quantification of these changes has been the real challenge for many years. Initial attempts to quantitatively measure cartilage volume were
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performed only in healthy subjects [7] or in animal models [8]. The recent improvements in image analysis have led to the reliable quantitative measurement of cartilage volume and thickness in both normal and disease conditions such as in OA. Cartilage volume quantification of the complete knee joint (femur and tibia) is now used for determining changes in this tissue over time (Figure 2) [9]. Research teams are now using the abovementioned specific MRI acquisitions combined with computer software to obtain valuable information on cartilage volume in normal and OA subjects [10-13]. Moreover, standard cartilage views can be anatomically segmented, allowing for the evaluation of cartilage volume and thickness in anatomical subregions as well as specific focal defects [9].

The reliability and precision of quantitative MRI (qMRI) assessments of any given radiological centre are first established with the use of phantoms

![Figure 2. Representation of grey-coded images of human osteoarthritic knee cartilage volume. Cartilage thickness was defined as the Euclidian distance between the bone-cartilage interface defined by the baseline image and the cartilage-surrounding tissue interface. Each thickness value was measured. A typical data set provides approximately 60,000 reading measurement points for the femur and 40,000 for the tibia. The volume is defined as volume between the bone-cartilage interface offset-map and its corresponding cartilage-synovium offset-map. Change in knee cartilage volume is obtained by subtracting follow-up cartilage volume from baseline volume. Maps showing the difference between baseline and one-year acquisition are displayed for femur and tibia and decreased thickness was seen mostly in the medial condyle and tibia.](image-url)
mimicking human tissue interfaces. Several acquisitions of these over short periods of time are used to assess the precision of both image acquisition and data extraction. These phantoms are also useful to assess any drift of the MR signal over a long time period combined with periodical machine maintenance. The principal issue is the assessment of distortion of the MRI equipment.

There have been demonstrations of the precision and reliability of the MRI technology for the assessment of change in cartilage volume of the knee over time in OA patients. For example, Eckstein et al. [14] published a study on precision errors in healthy volunteers under short term imaging conditions (acquisitions taken one after the other with joint repositioning), long term imaging conditions (acquisitions taken approximately over 9 months, but post-processed immediately one after the other), and re-segmentation (post-processing) of the same data sets spaced over 12 months. They found that long term precision errors (1.9 to 3.9 coefficient of variation [CV%]) were not significantly larger than short term acquisition errors (2 to 3.6 CV%). In addition, no systematic drift was observed, suggesting that scanner conditions had remained stable throughout this period. However, in this study semi-automated re-segmentation errors were somewhat higher over time. Further, excellent inter- and intra-reader reliability of such semi-automated MRI technology to quantify cartilage volume/thickness in patients with knee OA has been demonstrated by our group [13]. The objectives were to assess measurement reliability by determining the differences between readings of the same image made by the same reader two weeks apart (test-retest reliability), determining the differences between the readings of the same image by different readers (between-reader agreement), and determining the differences between the cartilage volume readings obtained from two MRIs of the same knee acquired a few hours apart (patient positioning reliability). MRI examinations of the knees of normal subjects, patients with different stages of symptomatic knee OA, and a subset of duplicate images were independently and blindly quantified by three readers using the imaging system. Between-reader agreement of measurements was excellent, as shown by intra-class correlation (ICC) coefficients ranging from 0.958 to 0.997 for global cartilage, 0.974 to 0.998 for the compartments, and 0.943 to 0.999 for the femur. Test-retest reliability of within-reader data was also excellent, as was patient positioning reliability, with Pearson correlation coefficients ranging from 0.978 to 0.999 and from 0.978 to 0.999, respectively.

Cross-sectional quantitative cartilage volume measurement

Estimates of cartilage thinning during normal aging (in the absence of OA) were derived from cross-sectional data obtained from healthy elderly
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Subjects without history of knee joint symptoms, trauma, or surgery (50 to 78 yrs; 11 men, 12 women) relative to a cohort of young, healthy subjects that met the same criteria (20 to 30 years; 49 men, 46 women) [15]. The authors reported an estimated 0.3% to 0.5% reduction in cartilage thickness per annum for all knee compartments. In the patella, women displayed a higher estimated loss than men, but no gender difference was found for the other compartments of the knee. Burgkart et al. [11] determined cartilage volume in OA patients prior to total knee replacement and estimated the loss by comparison with a group of healthy volunteers. They reported a difference of approximately 1300 mm$^3$ in the medial tibia in patients with varus OA, and differences of approximately 1800 mm$^3$ in the lateral tibia in patients with valgus or bi-compartmental OA. These values were found to exceed the precision error in the tibia of healthy volunteers and OA patients by a factor of >20:1. Recently, however, extensive age- and gender-specific reference data on normal volunteers have been published [15, 16], providing T- and Z-scores for the OA population, as currently used in the diagnosis of osteoporosis. One problem with this approach, however, is the relatively large inter-subject variability of cartilage volume in healthy individuals. Because of a weak correlation between cartilage volume and body height and weight but a much greater one with bone size [17], it has been suggested that cartilage volume should be normalized to the original bone interface area (before the onset of disease) to achieve better discrimination between OA patients and healthy subjects.

Optimization of cross-sectional analysis is particularly important for patient inclusion in longitudinal trials. Small cartilage volume alone does not appear to be a suitable selection criterion, because this would include subjects with small bone size rather than those with reduced cartilage thickness. This is particularly relevant as cartilage thickness and joint size have been shown to be not highly correlated [17].

Longitudinal quantitative cartilage volume measurements

Data on changes in cartilage volume from longitudinal studies have recently become available. Wluka et al. [12] quantified the changes in cartilage volume in the medial and lateral tibia of individuals with symptomatic and radiographic evidence of knee OA over a period of approximately two years. The mean loss of tibial articular cartilage was 5.3% per year. Age and body mass index (BMI) were also found to be weakly associated with cartilage (tibia) volume loss. The authors found no significant difference in the amount of relative (%) cartilage loss between women and men, and only a relatively low correlation between changes in the medial and
lateral tibia. Further analysis of subjects from the same cohort [18] revealed that the rate of relative (%) cartilage loss in the patella was significantly higher in women (5.3%) compared with men (3.5%). Interestingly, the authors found no significant association between change in the patella and both the medial and lateral tibia, suggesting different OA pathogenetic mechanisms. However, they reported that subjects with higher baseline pain scores displayed greater cartilage volume loss than those with lower pain scores, as did those with high BMI.

Another study by our group examined the progression of cartilage volume loss in patients with symptomatic knee OA over two years [19]. Knee OA progression (cartilage volume loss expressed as % of loss compared to the baseline value for each patient) computed at all the follow-up points was statistically significant: a mean of 3.8% of global cartilage loss (femur and tibia) and 4.3% for the medial compartment (medial femoral condyle and tibial plateau) at 6 months; 3.6% and 4.2% loss at 12 months; and 6.1% and 7.6% loss at 24 months. Using discriminatory function analysis, two groups were identified: slow and fast progressors. The risk factors identified to be associated with the fast progressors were female gender, high BMI, reduced range of movement of the study knee, greater knee circumference, and higher knee pain and stiffness scores as assessed by the Western Ontario and McMcMasters Universities Osteoarthritis Index (WOMAC) questionnaire. A second study [20] using a larger number of OA patients further identified 3 different populations according to cartilage volume loss: slow (with 2.3% global cartilage volume loss at 24 months), intermediate (7.2%), and fast (13.2%) progressors.

**Influence of other knee structure changes on OA cartilage volume loss**

Another advantage of MRI compared to conventional imaging technologies, is its ability to globally assess all major joint structures, including the cartilage (Figure 2), meniscus, bone marrow alterations (Figure 3), synovial (membrane and effusion), and ligaments.

Indeed, cartilage volume loss can be dependent on other structural damage such as meniscal damage or joint malalignment. The menisci transmit 50% to 90% of load over the knee joint, depending on knee flexion angle and femoral translation and rotation. The meniscus also contributes to knee joint proprioception and probably also to joint stability [21]. Cicuttini et al. [22] in a study comparing patients who had undergone surgical meniscectomy with controls and an average of 28 months follow-up, showed
that cartilage volume loss over time as assessed by qMRI was greater in patients who underwent partial meniscectomy. This result suggests the strong role of the meniscal apparatus in protecting cartilage, especially in older subjects or those suffering from obesity or joint instability. Biswal et al. [23] also looked at the risk factors for progressive cartilage loss in knee OA patients using MRI. Baseline and follow-up MRIs of the knee (mean 1.8 years apart) were done and cartilage volume loss was graded semi-quantitatively in the anterior, central, and posterior regions of the medial and lateral knee compartments. Data showed that meniscal and anterior cruciate ligament tears were associated with a more rapid cartilage loss. These authors also demonstrated that the central portion of the medial compartment had a more rapid progression of cartilage loss than the anterior or posterior areas. These data are a clear indication that cartilage loss in OA is not evenly distributed in the knee.

Another MRI study done by Berthiaume et al. [24] evaluating the impact of meniscal damage on cartilage volume loss assessed by MRI showed a strong and highly statistically significant association between the global cartilage (femur and tibia) volume loss and the presence of a severe medial meniscal extrusion. An even greater association was found between the medial meniscal extrusion and the loss of cartilage in the medial compartment.

The importance of other structural changes such as bone marrow hypersignal (Figure 3c) in assessing knee OA was first demonstrated by Felson et al. [25]. In this study, patients with knee OA had baseline assessments including MRI and fluoroscopically positioned radiography and were followed for 30 months. Progression was defined as a decrease over follow-up in medial or lateral joint space based on a semi-quantitative

**Figure 3.** Human knee cartilage in sagittal view acquired with a 1.5 Tesla magnet using fast imaging at steady state precession (FISP) acquisition with fat suppression. **a)** Meniscal tear (arrow), **b)** meniscal extrusion (arrow), **c)** bone marrow lesion (BML) (arrow).
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grading. Knees with medial bone marrow lesions (BML) showed a higher incidence of medial progression versus knees without lesions (odds ratio for progression, 6.5 [95% CI, 3.0 to 14.0]). These findings, which are in agreement with our group’s study [20], provide additional arguments to support the relationship between the cartilage volume loss and other anatomical knee changes. The latter study [20] demonstrated that the strongest predictors of cartilage volume loss in knee OA patients were the presence of severe meniscal extrusions, severe medial tear, and medial and/or lateral bone hypersignal along with clinical variables such as high BMI, weight, and age.

A new non-invasive synovial thickness scoring system using MRI was also recently developed [26], which accurately and reliably assessed the severity of synovitis in knee OA patients. The MRI sequences developed to evaluate the synovial tissue provide optimal visualization of both the medial and lateral compartments of the OA knee, where the most clinically relevant structural changes take place. This pivotal work was the first to enable a correlation between the severity of the synovial membrane inflammation and the loss of articular cartilage both using MRI. Moreover, it has clarified the likely role played by meniscal extrusion in the induction of synovitis.

Together, these data demonstrated that meniscal tear and extrusion are among the most significant risk factors associated with the progression of knee OA.

Clinical trials using qMRI as an outcome tool to evaluate anatomical knee structure

An important recently published two-year randomized multicentre trial using qMRI and X-rays explored the effects of a lipoxygenase and cyclooxygenase (LOX/COX) inhibitor for DMOAD properties in knee OA patients [27]. Quantitative MRI was used to assess changes in cartilage volume and X-rays (Lyon-Schuss) were used to measure changes in the mean and minimum JSW in the medial compartment. MRI data demonstrated that cartilage volume loss in the global and lateral knee compartment was significantly less in the LOX/COX group compared to the control (the non-steroidal anti-inflammatory drug Naproxen) group at 12 and 24 months, thus having a protective effect in knee OA patients. Patients with medial meniscal extrusion had greater loss of cartilage volume and the LOX/COX markedly reduced the cartilage volume loss at 12 and 24 months, demonstrating the importance of identifying meniscal structure lesions as an important co-factor of disease progression. In this
study, although the LOX/COX compound showed less reduction in the JSW than control, this did not reach significance. These findings clearly demonstrate the important limitation of standard radiographs compared to qMRI in investigating DMOAD effects. Moreover, both drugs were equally effective at reducing OA symptoms. These two outcomes are probably independent of each other, as pain is usually assessed in a relatively short time span while a longer follow-up is needed to appreciate the benefit of joint structural protection as assessed by MRI. Perhaps symptom evaluation should be redefined when evaluated together with joint structure. The American College of Rheumatology criteria for primary OA of the knee [28] are currently based on clinical and/or radiological findings. Since the cartilage is not vascularized or innervated, the pain experienced in OA is likely to originate from bone, synovial, capsule or ligament alterations. The “pure” anatomical cartilage volume loss over time, if chosen to define primary OA, may not be reflected at first by changes in symptoms, which considerably precede the radiological changes and may be accelerated by unsuspected concomitant meniscal damage. This is reflected by studies showing that change in pain level was weakly associated with cartilage volume loss at two years. It is therefore possible that redefining the symptom evaluation according to a longer period would show a stronger relationship between these two variables.

To address the question of the benefit of a DMOAD, a “hard” outcome such as preventing the occurrence of total knee replacement (TKR) could be targeted. In this line of thought, a recent study was performed to identify predictive factors for TKR in the abovementioned study [27] using the according-to-protocol (ATP) OA knee cohort [29]. The incidence of TKR was assessed blindly to the treatment following telephone interviews, and TKRs done in the time frame of 4-7 years following enrolment in the original study were used. Data revealed more TKRs within the control (Naproxen) group (61%) than in the LOX/COX group (39%). Furthermore, baseline score of BMLs in the medial compartment, medial JSW, presence of severe medial meniscal tear, medial meniscal extrusion, and C-reactive protein level were strong predictors of TKR. Changes at the end of the study (24 months) also yielded strong predictors: change in cartilage volume of the medial compartment and global knee, and WOMAC pain and function scores. Multivariate analysis further revealed that baseline severe medial meniscal tear and presence of a medial BML were the strongest independent long term predictors of TKR. In brief, this study shows that in the context of OA clinical trials, clinical data and structural changes identified by MRI allow prediction of a “hard” outcome such as TKR [29].
Comparing MRI with standardized knee radiograph measurements

Studies that have directly compared quantitative changes in cartilage volume using MRI to measurements of JSN in radiographs have produced conflicting results. A cross-sectional study by Cicuttini et al. [16] comparing cartilage volume in the tibia measured by MRI to radiologic grade (osteophytes and JSN) revealed that JSN, as graded from 0 (no disease) to 3 (most severe disease), was inversely correlated with the tibia cartilage volume as assessed by MRI. Such inverse relationship was even stronger while adjusting for age, sex and BMI. Gandy et al. demonstrated [30], in a study of knee OA over a three-year period, narrowing of JSW in weight-bearing extended radiographs of -0.21 mm while no significant change in cartilage volume was found by MRI in any of the knee compartments. They argued that radiography may be more sensitive than analysis of total cartilage plates by MRI because in radiographs, measurements are obtained in the central portion of the joint surface, where most of the changes may occur. However, it should also be kept in mind that the cohort was relatively small (n=11 patients) and that, in contrast to most other studies, the authors used a 1.0 T rather than 1.5 T magnet for their study, with relatively high associated precision errors. Conversely, our group [19] described no significant change in weight-bearing semiflexed radiographs in OA patients over two years, but reported a highly significant change in cartilage volume from MRI in both the medial and lateral tibiofemoral compartments. These findings were further reinforced from a larger cohort with knee OA [20].

MRI appears, therefore, to be significantly more sensitive in detecting volume change in the articular cartilage. It provides direct assessment of cartilage thickness and volume progression, while the JSW is an indirect measurement, which could be subject to a number of artefacts related to factors such as positioning, image acquisition, and changes in joint structure other than cartilage.

Fully automated qMRI assessment of knee OA structure

MRI-based quantitative knee joint structure assessments are and will be increasingly used for evaluation of the efficacy of a DMOAD. To date, only manual or semi-automated qMRI assessment methods have shown enough stability to produce cohort-scaled results. As a next generation tool, fully automated joint structure volume assessment solutions will enhance stability and reproducibility of MRI reading. In recent years, our group has developed
such fully automated segmentation systems for knee OA bone contours [31], as well as quantitative volume evaluation of cartilage [32] and synovial fluid [33].

The developed fully automated MRI method for bone contours relies on easy-to-gather input information from a single MRI acquisition [31]. A validation protocol performed over a large knee OA cohort comparing the developed automated method [31] to a validated semi-automated segmentation technology [9], provided excellent results with the evaluation criteria commonly used in this field. Data revealed that the average surface distance standard deviation was less than half a pixel. Similarly, the test–retest evaluation showed excellent reproducibility with an average of less than half a pixel resolution and maximum value of less than a pixel for the femur. The comparison between cartilage volumes using fully automated versus semi-automated bone surface shows no separability of the volume distributions between these two systems for both the femur and the tibia. In addition, for the cartilage volume, the Pearson correlation coefficients were excellent for both the femur and the tibia (r=0.99) as was the Dice similarity coefficient. In brief, this technology provides stable results and is robust to the variable MR image quality as reflected by the validation analyses performed on knee OA patients. Importantly, this technology also permits, for the first time automatically, the detection and quantitative evaluation of knee osteophyte volume.

For automated cartilage segmentation, a pivotal study assessing knee OA progression and validation experiments was recently reported [32]. The fully automated cartilage volume quantification demonstrated excellent correlations with semi-automated segmented cartilage volume, not only for the global cartilage but also for subregions of the knee. Correlation of cartilage volume and loss between two visits (12 months apart) also revealed excellent accuracy of automated cartilage segmentation of the pathologic knees. Test–retest validation showed a very low error measurement level, suggesting that the developed automated system is reliable and provides precise assessment of human OA knee cartilage volume. Since cartilage degradation is the hallmark of OA and its volume loss is related to the progression of the disease, such a fully automated method combined with the automated MRI method for bone contours would be useful not only for diagnosis, but also for clinical trials with patient follow-up.

Knee joint effusion is a common finding in OA patients and may be related to the activity of the disease. Therefore, non-invasive fully automated quantification of joint effusion volume in the knee would be a valuable tool for diagnostic, follow-up, and clinical studies. Recently, such an automated system for joint effusion volume quantification has been reported [33].
system was validated by external means, i.e. calibrated phantoms, manual MRI quantification, and direct aspiration. Data revealed excellent CV with a small (cylinder, 1.4%) and a large (sphere, 0.8%) calibrated phantom, and excellent correlations ($r=0.98$) between the automated and manual quantification of the OA knee joint effusion volume, as well as with direct aspiration ($r=0.88$).

The obvious advantage of these automated methods is the possibility of intensive and autonomous computation, enabling images from a large cohort of patients to be analyzed in a shorter time and, more importantly, increased reading stability. These methods may prevent major problems encountered with the current manual and semi-automated segmentation methods related to contrast, intensity, and gamma tuning for the image display, which have an important influence on the final segmentation contours. Moreover, they will also prevent intra- and inter-observer variations, the subjectivity of human intervention and errors due to fatigue, especially for large clinical trials. However, although such automated quantitative MRI evaluations are highly promising, the responsiveness to change under therapy must be further tested in a longitudinal study in view of its future application.

**MRI and identification of macromolecules in articular cartilage**

The concentration of glycosaminoglycan (GAG) in articular cartilage is also known to be an important determinant of the mechanical properties of this tissue. Concentrations of GAG have been explored by using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). In a recent study [34], tibias of patients undergoing total knee arthroplasty were imaged by dGEMRIC and the load response to focal indentation was measured as an index of cartilage stiffness at different test locations for each tibia. Overall, a high correlation was found between the dGEMRIC index (T1Gd) and local cartilage stiffness (Pearson correlation coefficients $r=0.90$). In brief, the results from this study demonstrate the importance of MRI in yielding spatial localization of GAG concentration in the evaluation of the mechanical properties of cartilage and suggest the possibility that this evaluation may be further improved by adding other MRI parameters that are sensitive to collagen, since the quality of the cartilage is dependent on the structural organization of the collagen network.

Moreover, Regatte et al. [35] reported the assessment of cartilage degeneration through GAG with the same efficiency as the dGEMRIC approach, but with a completely non-invasive technology. This technology
used a spin-lock pulse sequence allowing evaluation by T1p parameter, comparable with the T1 or T1Gd.

Another MRI acquisition technique, T2-mapping, was further shown to detect changes in cartilage water content. Liess et al. [36] demonstrated on healthy volunteers that reducing the water content of the patellar cartilage by repetitive knee bending can be quantified using a transverse relaxation time (T2) MRI sequence. Hence, the detection of small physiological changes in water content may help in the early diagnosis of OA.

T2 imaging was also suggested to be relevant for collagen variation assessment as discussed in an overview by Mosher et al. [37], which shows the relationship between cartilage T2 imaging and the cartilage water content, proteoglycan concentration, collagen concentration, or tissue anisotropy. Alternatively, the MR diffusion tensor imaging (DTI), could also be useful for detecting early changes in collagen fiber alignment, as DTI allows determination of the degree of diffusion anisotropy and the direction of local diffusion in tissues. Thus, by using DTI technology, Filidoro et al. [38], on a 9.4 T magnet field, were able to identify the orientation of collagen fibers in the patella.

**Conclusion**

The quantitative assessment of cartilage thickness and volume and other joint structure changes in OA is primarily to objectively evaluate the disease course as well as DMOAD treatment that may slow down OA tissue degradation. The problems faced a decade ago by clinical research that MRI technology must be based on readily available acquisition parameters easily reproducible in most available apparatus are now history. Data have shown such technology to be exportable to other centres with comparable MRI facilities, and can thus be used in multicentre clinical trials. Moreover, the fully automated quantification of joint structure opens the door to intensive and autonomous computation, enabling images from large scale studies to be reliably analyzed in a shorter time frame with high accuracy.

Because of the condition of the patients and the symptoms they experience, image acquisition should be performed in a time-wise fashion without compromising image quality. This is particularly critical for the quantification of disease progression over time. The future of OA research pertaining to prevention or repair of structural damage can be compared, to some extent, to the evolution experienced in the field of osteoporosis in the last few decades. In the beginning a significant bone loss was necessary to diagnose osteoporosis on plain radiographs. With the advent of
osteodensitometry, relatively small changes in bone mass can be detected and early diagnosis can be established. This outcome tool opened the door to clinical research on new therapies to slow or prevent bone mass loss. Everyone knows the impact of these medications on the outcome of osteoporosis today. Similarly, quantification of cartilage loss and the other joint structure changes seen in OA over time will improve the monitoring of OA and help to develop and test new interventions to prevent the progression of this extremely prevalent disease.

In conclusion, data have proven that MRI yields clear visualization of knee structure affected by OA and the superiority of the quantification of the damage by MRI over the standard imaging using radiographs has been demonstrated. The evaluation of knee OA using qMRI must be done in the context of whole organ assessment including meniscal damage, BML, and synovial membrane and effusion alterations. The recently developed fully automated qMRI will enhance the speed and reliability of the evaluation of the progression of joint structural damage. MRI technology should therefore be included in DMOAD clinical trials, used for early OA detection and treatment follow-up, and further employed for appraisal of the correlation between rapid knee structural changes as detected by qMRI and either short-term symptom changes (e.g. knee pain and function) or the prediction of long term hard outcomes, such as the occurrence of joint replacement.

References