Use magnetic resonance imaging to assess articular cartilage

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Abstract: Magnetic resonance imaging (MRI) enables a noninvasive, three-dimensional assessment of the entire joint, simultaneously allowing the direct visualization of articular cartilage. Thus, MRI has become the imaging modality of choice in both clinical and research settings of musculoskeletal diseases, particular for osteoarthritis (OA). Although radiography, the current gold standard for the assessment of OA, has had recent significant technical advances, radiographic methods have significant limitations when used to measure disease progression. MRI allows accurate and reliable assessment of articular cartilage which is sensitive to change, providing the opportunity to better examine and understand preclinical and very subtle early abnormalities in articular cartilage, prior to the onset of radiographic disease. MRI enables quantitative (cartilage volume and thickness) and semiquantitative assessment of articular cartilage morphology, and quantitative assessment of cartilage matrix composition. Cartilage volume and defects have demonstrated adequate validity, accuracy, reliability and sensitivity to change. They are correlated to radiographic changes and clinical outcomes such as pain and joint replacement. Measures of cartilage matrix composition show promise as they seem to relate to cartilage morphology and symptoms. MRI-derived cartilage measurements provide a useful tool for exploring the effect of modifiable factors on articular cartilage prior to clinical disease and identifying the potential preventive strategies. MRI represents a useful approach to monitoring the natural history of OA and evaluating the effect of therapeutic agents. MRI assessment of articular cartilage has tremendous potential for large-scale epidemiological studies of OA progression, and for clinical trials of treatment response to disease-modifying OA drugs.

Keywords: cartilage, knee, magnetic resonance imaging, osteoarthritis

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Introduction

Magnetic resonance imaging (MRI) provides high-spatial-resolution, multiplanar imaging and excellent tissue contrast. This enables a three-dimensional assessment of all components of the joint simultaneously, allowing direct visualization of articular cartilage. With the advances in techniques and development of dedicated sequences, MRI has become the imaging modality of choice in both clinical and research settings of musculoskeletal diseases, in particular osteoarthritis (OA), a chronic joint disease characterized by destruction and progressive loss of articular cartilage and clinical symptoms including pain, stiffness and impaired function.

Although OA is a major clinical and public health problem resulting in substantial burden to the individuals and society, the pathogenesis of OA has not been fully understood. Consequently, limited preventive strategies have been identified to modify the predisposing factors of OA, and no current treatments have been shown to slow disease progression, with end-stage symptomatic disease treated by joint replacement surgery. An accurate assessment of structural changes in articular

cartilage is required to monitor the progression of OA and evaluating the therapeutic response. The understanding of OA and the development of therapeutic interventions have been hampered by the lack of validated, noninvasive tools to quantify articular cartilage and assess the severity and progression of the disease. Early identification of disease has the potential to provide novel opportunities to trial both nonpharmacological and pharmacological (e.g. disease-modifying osteoarthritis drugs [DMOADs]) agents to help curtail the burden of this prevalent and debilitating disease.

The current gold standard for the assessment of OA in clinical and epidemiological settings is based on radiographs. This assumes that joint space narrowing or width may be used as a surrogate for articular cartilage. Although substantial advances have been made with radiographic techniques, the radiographic methods have significant limitations when used to measure disease severity and progression. Radiographs provide two-dimensional images of a three-dimensional structure, and only provide direct assessment of bony features. Radiographs are unable to delineate articular cartilage directly and thus are unable to detect early cartilage pathologies. Once radiographic changes are detected, significant disease is already present: with grade 1 joint space narrowing being detected, 11–13% of cartilage has been lost [Jones *et al*. 2004]. The measurement of joint space narrowing is prone to measurement error related to positioning of the joint, and its position respective to radiograph and source of radiation [Altman *et al*. 1996; Buckland-Wright *et al*. 1995; Ravaud *et al*. 1996]. This is of particular concern in multicentre studies and longitudinal studies. Radiographic grading provides a crude and insensitive method by which to assess disease progression, thus a larger sample size followed up for a prolonged period is required for studies examining radiographic progression of OA. Moreover, structures other than articular cartilage in the joint space may result in changes in joint space narrowing: meniscal extrusion has been shown to contribute to joint space narrowing independent of cartilage status [Adams *et al*. 1999; Gale *et al*. 1999].

There has been increasing interest in using MRI to examine joint cartilage as a measure of disease severity and progression of OA. In 1996, an expert consensus concluded that for knee OA, MRI would likely be useful, once validated methods of measurement are developed to measure articular cartilage [Altman *et al*. 1996]. Over the past decade, much work has been done in this area. MRI enables quantitative (cartilage volume and thickness) and semiquantitative assessment of articular cartilage, and recently the assessment of cartilage matrix composition, such as T1 relaxation time in rotating frame (T1rho), T2 relaxation time, and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), thus providing new insight into the natural history and determinants of cartilage pathologies. The emerging evidence suggests that MRI is able to show early morphological changes in articular cartilage related to OA, prior to the onset of radiographic disease. Evidence from MRI studies has suggested that there is a continuum from a healthy joint, through to the preclinical state, and ultimately to the changes of end-stage OA, at which time joint replacement is indicated. MRI provides accurate and reliable assessment of articular cartilage which is sensitive to change [Eckstein *et al*. 2006]. This suggests that using MRI cartilage morphology measures as the end point will reduce the number of participants needed in clinical trials and reduce the length of clinical trials to detect the treatment response to DMOADs with sufficient statistical power, having the potential to decrease the cost of clinical trials.

Quantitative assessment of articular cartilage

Cartilage volume

Cartilage is a three-dimensional structure. Cartilage volume can be measured from MR images [Cicuttini *et al*. 2000; Peterfy *et al*. 1994]. This has the theoretical benefit of being less subject to repositioning error than joint space width obtained from plain radiography, since cartilage is measured in three dimensions, as well as removing the effect of meniscal extrusion on apparent changes in joint space narrowing [Adams *et al*. 1999; Gale *et al*. 1999]. Although important in cross-sectional studies, this becomes more critical in longitudinal studies, where repositioning error will have a greater impact on study results.

Validation of cartilage volume measurement. Before using cartilage volume as an endpoint in studies, it requires validation: verification that cartilage measurement using MRI can measure cartilage volume accurately and reliably. This involves comparing the new measurement with a gold standard.

The face validity (i.e. the extent to which the MRI-derived results measure articular cartilage)

of the measurement of cartilage volume have been established by a number of studies, and the degree of accuracy has been shown to be similar for all cartilage surfaces of the knee [Burgkart *et al.* 2001; Cicuttini *et al.* 1999, 2000; Dupuy *et al.* 1996; Eckstein *et al.* 1998a, 1998b; Graichen *et al.* 2004; Peterfy *et al.* 1994; Pilch *et al.* 1994; Piplani *et al.* 1996; Sittek *et al.* 1996]. These studies established that MRI-derived cartilage volume measurement had high face validity using cadaveric and surgical specimens [Burgkart *et al.* 2001; Cicuttini *et al.* 1999, 2000; Dupuy *et al.* 1996; Eckstein *et al.* 1998b; Graichen *et al.* 2004; Peterfy *et al.* 1994; Pilch *et al.* 1994; Piplani *et al.* 1996; Sittek *et al.* 1996] and alternative imaging methods (CT arthrography) [Eckstein *et al.* 1998a], with random errors of 5–10%. There is no consistent or systematic underestimation or overestimation of cartilage volume. Thus, MRI-derived measurements of cartilage volume appear to be a valid method to measure knee cartilage. The resolution, signal-to-noise ratio and contrast-to-noise ratio are substantially improved using a 3.0-T imaging system, resulting in higher accuracy in quantifying cartilage volume compared with a 1.5-T system [Bauer *et al.* 2006; Eckstein *et al.* 2005].

Reproducibility of cartilage volume measurement. To be a useful tool, cartilage volume not only has to be valid, but also be reproducible. Reproducibility is the extent to which measurement of the phenomenon of interest provides the same results upon repeat applications under the same circumstances. This may be tested using the test–retest method. It can be assessed for both intra-observer (intrarater) reliability, where one observer measures disease on the same image on different occasions, and inter-observer (interrater) reliability, where more than one observer measure disease at different points in time. This measures the extent to which the test is free of random error (subject variation, instrument variation and observer variation). MRI-derived measurement of knee cartilage volume has been assessed by many investigators in different compartments of the knee and shown to have high reproducibility [Cicuttini *et al.* 1999, 2000; Dupuy *et al.* 1996; Eckstein *et al.* 1998b; Marshall *et al.* 1995b; Peterfy *et al.* 1994; Piplani *et al.* 1996; Sittek *et al.* 1996]. The interobserver reproducibility ranges from 0.4% to 7.8% (coefficient of variation [CV]); the intra-observer reproducibility from 0.3% to 6.4% (CV), and the image re-image reproducibility from 1.1% to 9.7% (CV). Raynauld and colleagues reported high reproducibility of MRI cartilage volume measurement, by assessing the inter-reader agreement, the test–retest reliability, and the patient positioning reliability on 48 MR examinations of the knee from normal subjects and patients with different stages of symptomatic knee OA [Raynauld *et al.* 2003]. The interreader agreement of measurements was excellent, as shown by intraclass correlation coefficients (ICCs) 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 femoral condyles. The test–retest reliability of intrareader agreement was excellent, with Pearson correlation coefficients ranging from 0.978 to 0.999. The patient positioning reliability was also excellent, with Pearson correlation coefficients ranging from 0.978 to 0.999 [Raynauld *et al.* 2003]. Moreover, cartilage volume measured at subregions of the joint surface may reduce the precision errors relative to those from measuring the entire cartilage plate [Kshirsagar *et al.* 1998]. Cartilage volume measurement using a 3.0-T imaging system tends be more reproducible than at 1.5-T system and may therefore provide superior ability to detect changes in cartilage status over time and to determine responses to treatment with structure-modifying drugs [Eckstein *et al.* 2005].

Sensitivity to change of cartilage volume measurement. Although articular cartilage can be seen with proper acquisition sequences, the quantification of cartilage volume change has been a challenge due mainly to postscan processing times. In OA, loss of cartilage volume may be accelerated, being a multifactorial phenomenon which may precede, accompany and/or result from other structural changes within the joint.

Eckstein and colleagues analysed the long-term and resegmentation precision of quantitative cartilage measurement. They found scanner drift and changes in imaging or patient conditions were not a critical problem in quantitative cartilage analysis [Eckstein *et al.* 2002]. The study suggested that in longitudinal studies, image analysis of sequential data should be performed within the same postprocessing session. They concluded that under these conditions, quantitative cartilage measurement is a very powerful method to assess structural cartilage changes in OA [Eckstein *et al.* 2002]. MRI also provides a far more sensitive measure of change in cartilage volume than the joint radiograph, with 11–13% of cartilage volume being lost before the first changes of radiographic joint space narrowing can be detected [Jones *et al.* 2004]. Several studies have reported

data on the change in cartilage volume in longitudinal studies, showing that measurement of knee cartilage volume is sensitive to change in both normal subjects [Hanna *et al*. 2005; Wluka *et al*. 2004a] and those with OA or at high risk of OA [Cicuttini *et al*. 2002a, 2002b; Raynauld *et al*. 2004; Wluka *et al*. 2002b]. In healthy postmenopausal women without clinical knee OA, tibial cartilage volume decreases on average by 2.4% per year [Wluka *et al*. 2004a]. In healthy middle-aged men, tibial cartilage volume reduces by 2.8% per year [Hanna *et al*. 2005]. Wluka and colleagues reported an annual tibial cartilage volume loss rate of 5.3% in patients with symptomatic and radiographic knee OA [Wluka *et al*. 2002b]. With the same cohort, Cicuttini and colleagues reported the higher patellar cartilage volume loss rate in women (5.3%) compared with men (3.5%) [Cicuttini *et al*. 2002a]. Raynauld and colleagues reported cartilage volume loss rate (period estimate) at a series of follow-up time points: 3.8% for global cartilage volume loss and 4.3% for medial compartment cartilage volume loss at 6 months, 3.6% and 4.2% at 12 months, and 6.1% and 7.6% at 24 months. Furthermore, discriminant function analysis identified 2 groups of patients, 21 patients progressed slowly (<2% of global cartilage volume loss) and 11 patients progressed rapidly (>15% of global cartilage volume loss), over the 2 years of study [Raynauld *et al*. 2004]. This study detected cartilage volume loss in the absence of changes in radiographic joint space narrowing, suggesting MRI is more sensitive to change than radiograph [Raynauld *et al*. 2004]. Cicuttini and colleagues reported a rate of tibial cartilage volume loss of 4.1% per year in a sample of participants undergoing partial meniscectomy [Cicuttini *et al*. 2002b].

Cartilage thickness

Whilst many authors have examined volume as an outcome measure, others have investigated cartilage thickness [Cohen *et al*. 1999; Eckstein *et al*. 1996, 1997, 1998a; Graichen *et al*. 2004; Kladny *et al*. 1996; Marshall *et al*. 1995a; Sittek *et al*. 1996]. Although this may appear an attractive measure, being a one-dimensional estimate of a three-dimensional structure, it shares one of the shortcomings of the use of joint space width as a measure of disease severity in that it may be more prone to repositioning error than cartilage volume. It is also sensitive to errors related to partial volume averaging, when a single measurement is used. Theoretically, this measure has the problem of ensuring the same thickness is measured on subsequent occasions. The method of coregistration of images may be used to ensure that this occurs. This adds significantly to the technical expertise and cost required for this measurement.

Validation of cartilage thickness measurement. Cartilage thickness has been investigated as an alternative and time-saving measure of articular cartilage. Although there are methodological issues including the difficulty of defining the section to be measured, it has been established that MRI-derived measurements of cartilage thickness and cartilage thickness pattern had high validity using cadaveric and surgical specimens and alternative imaging methods (CT arthrogram or stereophotogrammetry), comparable with cartilage volume [Cohen *et al*. 1999; Eckstein *et al*. 1996, 1997, 1998a; Graichen *et al*. 2004; Kladny *et al*. 1996; Marshall *et al*. 1995a; Sittek *et al*. 1996]. In quantifying cartilage thickness, central and weight-bearing regions of the femoral condyles can provide more accurate measurement than boundary and non-weight-bearing regions [Koo *et al*. 2005]. MRI-derived measurements of cartilage thickness appear to be a valid method to measure knee cartilage. Cartilage thickness measurement using a 3.0-T imaging system showed nonsignificant difference from measurements using a 1.5-T system [Eckstein *et al*. 2005; Kornaat *et al*. 2005b].

Reproducibility of cartilage thickness measurement. One centre has attempted reproducibility studies of cartilage thickness [Eckstein *et al*. 1996, 1998a, 1998b]. This has used highly sophisticated mapping to measure thickness profiles. It has not been tested longitudinally, or with coregistration, to ensure cartilage thickness at the same position were compared. This is a potential pitfall when cartilage thickness is used as an outcome measure in longitudinal studies. The results of these studies suggest misclassification of thickness occurs in approximately 33% of cases, in all studies and cartilages. A second centre performed intra-observer and interobserver reproducibility studies [Karvonen *et al*. 1990]. This group reported an intra-observer variability of 3.2–10.5% (CV). Interobserver variability ranged between 5.4–29.7% (CV). The reproducibility of this measure is less than cartilage volume. Whilst some early investigators used this measure alone [Karvonen *et al*. 1990, 1994], more recent studies use thickness as an outcome measure in addition to volume measurements.

Sensitivity to change of cartilage thickness measurement. Cartilage thickness naturally decreases with normal aging, with an annual reduction of 0.3–0.5% [Hudelmaier *et al.* 2001, 2003]. In young adults with acute anterior cruciate ligament injury, over 2 years, significant cartilage thinning is observed in the trochlea of the femur at a rate of 4.3%, while significant cartilage thickening is observed in the central medial aspect of the femur at a rate of 2.7% [Frobell, 2011]. In patients with radiographic knee OA, over 12 months, the mean cartilage thickness reduction in the central subregion of medial femoral condyle is 12 μm in knees without pain, 27 μm in those with infrequent pain and 54 μm in those with frequent pain [Eckstein *et al.* 2011]. In a subsample of the OA Initiative progression subcohort, the mean cartilage thickness reduces by 2.8% in the central aspect of medial femoral condyle, 1.9% in the total medial femoral condyle, 0.9% in the central medial tibia and 0.5% for the entire medial tibia [Wirth *et al.* 2009]. In patients with radiographic knee OA, the total tibiofemoral cartilage thickness reduces by 0.8–1.3% in the first year and by 0.7–0.8% in the second year [Wirth *et al.* 2011]. There is data suggesting that the mean cartilage thickness over the entire subchondral bone area tend to be more reproducible and more sensitive to change than cartilage thickness over the cartilaginous area or maximum cartilage thickness [Hudelmaier *et al.* 2010]. Cartilage thickness has shown similar sensitivity to assess cartilage loss compared with cartilage volume in a clinical trial [Raynauld *et al.* 2008].

Subregional measurement of cartilage volume and thickness

There has been interest in measuring cartilage volume and thickness in subregions of the femoral and tibial cartilage plates. In a longitudinal study of 107 patients with knee OA performed by Pelletier and colleagues subregion analysis revealed that the greatest cartilage volume loss at 24 months was found in the central area of the medial tibial plateau (15%) and of the medial femoral condyle (12%) [Pelletier *et al.* 2007]. Recent studies demonstrated that the greatest rate of cartilage volume and thickness loss was observed in the central medial femoral condyle [Eckstein *et al.* 2009; Hunter *et al.* 2009; Wirth *et al.* 2009]. However, in line with other investigation [Raynauld *et al.* 2008], the sensitivity to change in the subregions is not consistently higher than in the total cartilage plates across studies, owing to the high standard deviation of the subregional measurements. Subregional assessment of cartilage may have missed the effect of intervention [Raynauld *et al.* 2008]. Thus, the potential of gaining statistical power with the use of cartilage volume and thickness change in knee subregions as an outcome would be negated by high interpatient variability [Raynauld *et al.* 2008]. The spatial heterogeneity of cartilage loss in OA patients may provide an explanation why subregional assessment of cartilage does not show a higher sensitivity to change. There is evidence that knee alignment determines the patterns of cartilage loss in the medial *versus* lateral compartment [Eckstein *et al.* 2008; Sharma *et al.* 2008] and that local biomechanical environment may be responsible for certain subregions to progress faster than others in certain subjects [Roemer *et al.* 2009]. Furthermore, in contrast to weight-bearing radiographs, MRI is non-weight-bearing, thus the central regions on knee MRIs may not be anatomical and may not be the weight-bearing regions particularly when there is malalignment.

Shortcomings of current methods of quantifying articular cartilage

Neither cartilage volume nor thickness measurements can assess the quality of cartilage present. This has been raised as a significant concern in cross-sectional studies, since theoretically, and in animal models, cartilage change in OA has been shown to be biphasic, with cartilage swelling occurring early, prior to cartilage thinning and loss [Calvo *et al.* 2001; Watson *et al.* 1996]. Histopathologically, the swelling of cartilage detected by MRI correlates with depletion in matrix proteoglycans and cellular loss, which are closely related to the progression of OA at the earliest stages [Calvo *et al.* 2004]. Longitudinal studies are less prone to this bias as swollen cartilage will have faster rates of loss. However, attempts to date have been unable to correlate cartilage quality with its appearance on MRI.

Semiquantitative assessment of articular cartilage

A number of scoring methods have been used to quantify regional cartilage loss, identifying irregularities of the cartilage. One such scoring method is that of cartilage defects. Cartilage defects are identifiable using MRI where the cartilage surface or the cartilage adjacent to bone is irregular, or where there is loss of cartilage thickness [Ding

et al. 2005c]. Histologically, these lesions are highly correlated with the Mankin scale for grading cartilage [McGibbon and Trahan, 2003].

Validity of cartilage defects measurement

Several studies have examined the diagnostic performance (sensitivity and specificity) of MRI-detected cartilage lesions using different acquisition sequences against surgically confirmed cartilage lesions and arthroscopy [Bredella *et al*. 1999; Disler *et al*. 1996; Duc *et al*. 2007, 2008; Kawahara *et al*. 1998; Kijowski *et al*. 2009, 2010; Murphy, 2001; Wong *et al*. 2009; Yoshioka *et al*. 2004]. The diagnostic performance is highest on patellar cartilage and lowest on lateral tibial cartilage, and is higher for deep cartilage lesions than for superficial lesions. Using a 1.5-T imaging system, the sensitivity ranges between 40% and 94%, and the specificity ranges between 70% and 100%. With a 3.0-T imaging system, the sensitivity ranges between 66% and 80%, and the specificity ranging between 80% and 97%. Although some studies have shown improved diagnostic performance of 3.0-T MRI protocol for evaluating cartilage defects compared with 1.5-T protocol [Fischbach *et al*. 2005; Kijowski *et al*. 2009; Link *et al*. 2006; Masi *et al*. 2005; Wong *et al*. 2009], there are significant overlaps in the sensitivity and specificity between 3.0-T and 1.5-T MRI protocols and some differences are not significant [Kijowski *et al*. 2009; Link *et al*. 2006].

Various MRI pulse sequences have been used for the assessment of cartilage defects, which has led to debates as per the choice of appropriate pulse sequences for MRI-based semiquantitative assessment of cartilage defects in OA research [Hayashi *et al*. 2010]. Similar overall diagnostic performance (relatively high sensitivity and specificity) for the detection of focal cartilage defects have been shown for fat-suppressed T1-weighted spoiled gradient recalled acquisition at steady state (SPGR) [Disler *et al*. 1996; Recht *et al*. 1996; Yoshioka *et al*. 2004], fat-suppressed T2-weighted fast spin echo (FSE) [Bredella *et al*. 1999; Broderick *et al*. 1994; Kawahara *et al*. 1998; Yoshioka *et al*. 2004], selective water-excitation SPGR [Mohr *et al*. 2003], dual echo steady state (DESS) [Woertler *et al*. 2000], and fat-suppressed driven equilibrium Fourier transform (DEFT) [Yoshioka *et al*. 2004]. Although SPGR sequences provide high spatial resolution, these sequences are vulnerable to artefacts (motion artefacts due to long imaging time and susceptibility artefacts). These should be considered after previous surgery, in particular after cartilage repair procedures [Link *et al*. 2007]. Despite the assessment of cartilage defects using SPGR sequences which may entail additional measurement error and misclassification due to these vulnerabilities, cartilage defects measured using these sequences have been associated with clinically important outcomes such as pain, radiographic OA, cartilage volume loss, cartilage breakdown markers, and knee replacement surgery in multiple cross-sectional and longitudinal studies [Ding *et al*. 2007b].

Reproducibility of cartilage defects measurement

For the assessment of cartilage defects, the intra-observer reliability (expressed as ICC) was 0.89–0.90, and the interobserver reliability (expressed as ICC) was 0.85–0.90 [Ding *et al*. 2005c]. For the assessment of cartilage lesions using Whole-Organ MRI Score, the interobserver agreement (expressed as ICC) was >0.98 [Peterfy *et al*. 2004]. The intra-observer reproducibility (expressed as ICC) of another scoring system, the Knee OA Scoring System, was 0.76–0.96, and the interobserver reproducibility was 0.63–0.91 [Kornaat *et al*. 2005a].

Sensitivity to change of cartilage defects measurement

In a study of 43 patients over 1–5 years (mean 1.8 years), among the cartilage lesions present at baseline, 12% were not detectable at follow up, 6% regressed to a lower grade, 32% remained the same grade and 50% progressed to a higher grade. There were 84 new lesions during the study period [Biswal *et al*. 2002]. In a study of 86 participants without knee OA, Wang and colleagues reported that over 2 years the cartilage defect score increased, and that the medial tibiofemoral, lateral tibiofemoral and patellar cartilage defect score increased in 63%, 65% and 36% of the subjects, remained unchanged in 32%, 30% and 46% of the subjects and decreased in 5%, 5% and 18% of the subjects, respectively [Wang *et al*. 2006]. In a convenience midlife sample of 325 subjects, over 2.3 years, patellar cartilage defect score increased significantly, 12%, 13% and 22% of subjects had an increase in cartilage defect scores, whereas 13%, 12% and 13% of subjects had a decrease in cartilage defect scores at the medial, lateral and patellar sites, respectively [Ding *et al*. 2005a]. Overall, 33% of the subjects had a

worsening (≥1 point increase) and 37% of the subjects had an improvement (≥1 point decrease) in cartilage defect score in any knee compartment during 2.3 years [Ding *et al.* 2006]. A study of symptomatic OA patients found increased cartilage defect score over the 2 years, and the heterogeneity with 81% progressing, 15% remaining stable and 4% regressing [Davies-Tuck *et al.* 2008]. It may be that the improvement in cartilage defects is, at least in part, attributable to measurement issues, however since cartilage defects had to be present on ≥2 consecutive slices [Ding *et al.* 2005c], it seems unlikely that this is due to measurement error alone in multiple independently assessed cohorts. These data suggest that there may be some repair of articular cartilage [Buckwalter and Mankin, 1998; Caplan *et al.* 1997] which decreases with increasing age.

Assessment of cartilage matrix composition

Although MRI-derived quantitative and semi-quantitative assessments of cartilage morphology have provided a useful tool to monitor cartilage loss and disease progression in OA, there is significant interest in using MRI to detect very early cartilage changes, prior to the morphological changes. Cartilage matrix composition can be assessed by MRI using several techniques, including T1rho, T2 relaxation time and dGEMRIC, which have been shown to be sensitive to early cartilage damage and a potential early marker for degenerative joint disease.

Using animal models and cartilage explants, T1rho is strongly correlated with changes in proteoglycan content [Akella *et al.* 2001; Regatte *et al.* 2003; Wheaton *et al.* 2004, 2005], and increase in T1rho is correlated with proteoglycan loss [Duvvuri *et al.* 2002], suggesting T1rho could be used as a method of quantifying proteoglycan changes in early stage OA. *In vivo* reproducibility of average T1rho of patellar cartilage was found to be 5% (CV) [Pakin *et al.* 2006]. In anterior cruciate ligament-injured knees, T1rho significantly increased in the posterolateral tibia and persisted 1 year after anterior cruciate ligament reconstruction, and T1rho of weight-bearing medial tibiofemoral cartilage was significantly elevated at 1 year after the surgery [Li *et al.* 2011]. Patients with OA patients showed significant elevation in T1rho compared with asymptomatic controls, and the T1rho was associated with the degree of cartilage degeneration [Li *et al.* 2005; Regatte *et al.* 2004]. These findings suggest that T1rho may be a promising clinical tool for OA detection and treatment monitoring.

In vivo, increasing T2 relaxation time is associated with the distribution of cartilage water and it is sensitive to small water content changes [Liess *et al.* 2002]. Aging has been shown to be associated with an asymptomatic increase in T2 of the transitional zone of articular cartilage. The diffuse increase in T2 in senescent cartilage is different in appearance than the focally increased T2 observed in damaged articular cartilage [Mosher *et al.* 2000]. When subjects with OA were compared with those without OA, femoral and tibial cartilage T2 values were higher in those with OA compared with healthy subjects [Dunn *et al.* 2004; Stahl *et al.* 2007]. However, no significant difference in T2 value was seen when those with mild and severe OA were compared [Dunn *et al.* 2004]. Similar results were shown in another study that found no differences in T2 values across the Kellgren–Lawrence grades of OA [Koff *et al.* 2007]. A longitudinal study examining change in women with and without OA showed no significant change in T2 values over 1 year in either group [Stahl *et al.* 2007]. These results indicate whilst T2 relaxation time differs in those with and without OA, it is not a sensitive marker of radiographic severity thus does not help to differentiate between mild and more severe OA. However, in contrast, in a group with and without OA, T2 values correlated with both clinical symptoms and cartilage morphology (cartilage volume and thickness), particularly in the medial compartment [Dunn *et al.* 2004]. This suggestion of clinical significance warrants further investigation.

Some studies compared the sensitivity of T1rho and T2 relaxation time. In a study of 10 healthy volunteers and 9 OA patients, a significant difference was observed in T1rho within patellar and femoral cartilage between the 2 groups. Although a significant correlation was found between T1rho and T2 relaxation time, the difference of T2 was not significant between controls and OA patients [Li *et al.* 2005]. Another study also found T1rho was superior to T2 in differentiating early OA from normal cartilage, although both T1rho and T2 values were significantly higher in early OA patients compared with healthy subjects [Stahl *et al.* 2009]. In an animal model, while T2 relaxation rates varied randomly without any particular trend, yielding a poor correlation with sequential depletion of proteoglycan, there was excellent linear correlation between the percentage

of proteoglycan and the T1rho relaxation rate, suggesting T1rho-weighted imaging, rather than T2-weighted imaging, is sensitive to sequential depletion of proteoglycan in bovine cartilage and can be used to quantify proteoglycan-induced changes [Regatte *et al*. 2002]. In cartilage specimens obtained from total knee replacement surgery with various clinical grades of OA, all cartilage specimens showed elevated T1rho and T2 relaxation times compared with healthy cartilage tissue. T1rho showed a higher dynamic range (>100%), and was correlated with the degree of cartilage degeneration. However, T2 relaxation times showed lower dynamic range [Regatte *et al*. 2006]. These data suggest that T1rho relaxation mapping is a sensitive noninvasive marker for quantitatively predicting and monitoring the status of macromolecules in early OA. The higher dynamic range of T1rho can be exploited to measure even small macromolecular changes with greater accuracy compared with T2 [Regatte *et al*. 2006].

dGEMRIC involves the intravenous injection of MRI contrast agent and the acquisition of a T1 map to allow a quantitative assessment of the glycosaminoglycan content within the cartilage, where the contrast agent is distributed in higher concentration in areas with lower glycosaminoglycan content. After application of gadolinium, the variations in T1 reflected about 50% variations in glycosaminoglycan, suggesting that dGEMRIC has potential for monitoring glycosaminoglycan content of cartilage *in vivo* [Bashir *et al*. 1997]. The dGEMRIC measurement of glycosaminoglycan has been validated against the reference standards of histological and biochemical measurement of glycosaminoglycan content [Bashir *et al*. 1999; Trattnig *et al*. 1999]. The T1 measurement in dGEMRIC is referred to as the dGEMRIC index. In 31 patients with knee OA, compartments without joint space narrowing had a higher dGEMRIC index than those with any level of narrowing. In knees with one unnarrowed (spared) and one narrowed (diseased) compartment, the dGEMRIC index was greater in the spared *versus* the diseased compartment. In spared compartments, there was a trend toward a lower dGEMRIC index with increasing Kellgren–Lawrence radiographic severity grade. There was a range of dGEMRIC values in the spared compartments within a given Kellgren–Lawrence grade, demonstrating biochemical differentiation of disease in radiographically comparable compartments. Valgus-aligned knees tended to have lower dGEMRIC values laterally and varus-aligned knees tended to have lower dGEMRIC values medially; as a continuous variable, alignment correlated with the lateral:medial dGEMRIC ratio. These data suggest the biochemical information provided by dGEMRIC scans may improve the differentiation of disease status within a given radiographic grade, especially in early OA [Williams *et al*. 2005]. Importantly, recent data showed low dGEMRIC index at baseline was predictive of the development of knee OA, suggesting the role of dGEMRIC index as a clinically relevant measure of cartilage integrity [Owman *et al*. 2008].

However, data is limited on the longitudinal assessment of these compositional measures of articular cartilage. Although these compositional measures may play an important role in detecting early cartilage changes before cartilage defects occur, the natural course of these measures and their relationship with cartilage morphological changes and clinical outcomes warrant further investigation.

Association between MRI cartilage measures and radiographic features

Since radiographic joint space narrowing is used as a surrogate measure of articular cartilage, it would be expected that MRI-derived cartilage assessments are associated with radiographic features. However, the evidence has been conflicting. Plain radiography is insensitive to early changes such as the development of cartilage defects and early cartilage loss that are unequivocally occurring prior to any radiographic diminution of the joint space. Whilst joint space narrowing and joint space width have been related to cartilage volume, longitudinal studies suggest that changes in joint space narrowing and joint space width are less sensitive in detecting cartilage loss than MRI [Raynauld *et al*. 2004, 2006].

A cross-sectional study by Cicuttini and colleagues showed a strong negative, linear association between medial and lateral tibial cartilage volume and increasing grade of joint space narrowing, and that the inverse relation was even stronger when adjusting for age, gender and body mass index [Cicuttini *et al*. 2003b]. In a 1-year longitudinal study, Bruyere and colleagues reported a moderate but significant association between changes in joint space narrowing and changes in cartilage volume and thickness patients

with knee OA [Bruyere *et al.* 2007]. Recently Pelletier and colleagues found, in patients with knee OA over 2 years, there was a significant correlation between reduction in joint space width and cartilage volume loss in the central weight-bearing area of the condyles and the plateaus as well as in the medial compartment [Pelletier *et al.* 2007]. Cartilage defects have been shown to be significantly associated with radiographic features of OA [Boegard *et al.* 1998; Brandt *et al.* 1991; Link *et al.* 2003]. In a study of 224 patients with symptomatic knee OA, cartilage loss assessed by semiquantitative MRI grading score was associated with joint space narrowing [Amin *et al.* 2005]. Kellgren–Lawrence score has been shown to be correlated with the grade of cartilage lesions [Link *et al.* 2003].

However, the study by Gandy and colleagues observed a 0.21 mm reduction in joint space width in weight-bearing extended radiographs found no significant cartilage volume change in any of the knee compartments [Gandy *et al.* 2002]. Raynauld and colleagues found no significant change in weight-bearing semiflexed positioned radiographs in OA patients over 2 years, but reported significant cartilage volume change in the medial and lateral femorotibial compartment. There was no significant correlation between baseline joint width and cartilage volume in the medial compartment, and between cartilage volume loss and radiographic changes over 2 years [Raynauld *et al.* 2004].

Fractal analysis of trabecular bone texture on radiographs has been shown to be a promising approach for assessing early knee OA [Kraus *et al.* 2009; Wolski *et al.* 2010, 2011]. In subjects without radiographic knee OA, trabecular bone texture in the proximal tibia is different between those with and without tibiofemoral cartilage defects, where trabecular bone texture roughness is greater in those with cartilage defects than in those without [Wolski *et al.* 2011]. These findings suggest a potential role of MRI cartilage assessment in studies evaluating new radiographic features.

Association between MRI cartilage measures and clinically important outcomes

Cartilage measures and symptoms

A number of MRI studies have demonstrated significant relationships between cartilage structural changes and knee pain. Cartilage volume loss has been associated with WOMAC pain changes over 24 months in patients with knee OA [Raynauld *et al.* 2006]. In a cross-sectional study of 133 postmenopausal females, alterations in patella volume were associated with pain, function and global scores of the WOMAC. In participants with more knee pain, there was an association with reduced patella cartilage volume [Hunter *et al.* 2003]. A longitudinal study of 117 subjects with knee OA over 2 years demonstrated a relationship between baseline cartilage volume and knee symptoms (WOMAC pain, stiffness and function scores), and a correlation between the loss of cartilage volume over 24 months and the worsening of symptoms [Wluka *et al.* 2004b]. This study suggested that although cartilage is not a major determinant of symptoms in knee OA, it does relate to symptoms [Wluka *et al.* 2004b]. One study found in patients with OA the grades of cartilage lesions rated from MRI were associated with clinical symptoms including pain, stiffness and limited function assessed by WOMAC scores [Link *et al.* 2003]. Full-thickness cartilage defects accompanied by subchondral bone defects are associated with pain in OA [Sowers *et al.* 2003]. The correlation between knee pain and cartilage defects has been reported in particular when the defect is moderate to severe (grade 2–3) [Zhai *et al.* 2006, 2007].

However, there are a few studies which found no associations between longitudinal cartilage change and worsening of symptoms as determined by WOMAC score [Phan *et al.* 2006; Raynauld *et al.* 2004]. Zhai and colleagues found in both younger and older adults that cartilage volume was not associated with knee pain [Zhai *et al.* 2006, 2007]. These data suggest that pain in knee OA may arise from a multitude of factors and is likely to originate from structures other than cartilage that are innervated by nociceptors including subchondral bone, meniscus, synovium, capsule or ligaments.

Cartilage measures and joint replacement

Joint replacement is considered a surrogate marker of end-stage symptomatic OA. In those with symptomatic knee OA, a higher cartilage defect score is associated with a sixfold increased risk of knee joint replacement over 4 years [Wluka *et al.* 2005]. Similarly, the rate of tibial cartilage volume loss over 2 years is an independent predictor of joint replacement, reporting a 20% increase in risk of undergoing joint replacement

over 4 years for every 1% increase in the rate of cartilage volume loss. When those in the top tertile of tibial cartilage volume loss were compared with those in the bottom tertile, they had a 7.1-fold increased risk of knee replacement [Cicuttini *et al*. 2004].

Role of MRI cartilage measures in understanding risk factors for OA and prevention of OA

The increased knowledge of the significance of different structural changes in OA has enabled better understanding of the risk factors for OA and novel approaches to preventing OA. This has been made possible by the use of sensitive measures of articular cartilage, enabling the examination of early cartilage alterations prior to the presence of radiographic disease.

Obesity

Obesity has been recognized as the most important modifiable risk factor for OA [Felson *et al*. 2000]. Obesity has been shown to influence MRI-assessable features of OA, which may in turn affect the risk of knee OA. Emerging evidence suggests that the means by which obesity affects joint health is likely to involve both biomechanical and metabolic mechanisms. Biomechanically, obesity increases the risk of OA directly through the increasing load on joints [Felson *et al*. 2000]. Metabolic factors are the product of adipose tissue, now considered an endocrine organ [Calabro and Yeh, 2007]. Adipose tissues release many factors, including pro-inflammatory cytokines such as tumour necrosis factor (TNF-α) and interleukin-6, and adipokines, such as leptin, adiponectin and resistin [Pottie *et al*. 2006]. Both TNF-α and interleukin-6 have been implicated in cartilage destruction in OA [Evans, 2005; Malemud, 2004], while leptin is a key regulator of chondrocyte metabolism and plays an important role in the pathophysiology of OA [Dumond *et al*. 2003]. Chondrocytes from joint cartilage have been shown to express leptin receptors [Dumond *et al*. 2003; Figenschau *et al*. 2001], which, when stimulated, produce nitric oxide, leading to inflammatory alterations in cartilage including phenotype loss of chondrocytes, apoptosis and metalloproteases activation [Kim *et al*. 2002; Otero *et al*. 2003].

Obesity, assessed by increase weight and body mass index, has been shown to be associated with reduced cartilage volume [Cicuttini *et al*. 2003a; Ding *et al*. 2003; Nishimura *et al*. 2005; Raynauld *et al*. 2004; Teichtahl *et al*. 2009b] but more consistently with increased cartilage defects [Anandacoomarasamy *et al*. 2009; Ding *et al*. 2005b, 2008; Hanna *et al*. 2007; Teichtahl *et al*. 2008]. However, body mass index as a measure of obesity, does not account for the pattern of fat distribution or body composition: it does not discriminate adipose from nonadipose body mass [Roubenoff, 1996]. Studies on body composition and knee cartilage provide new insight into the mechanism by which obesity is associated with an increased risk of knee OA. In a longitudinal study of healthy, middle-aged adults without knee OA, loss of muscle mass was associated with an increased loss of medial and lateral tibial cartilage volume over 2 years [Cicuttini *et al*. 2005]. A cross-sectional study of 297 adults with no clinical knee OA found that greater fat-free mass was associated with increased cartilage volume, while greater fat mass was associated with reduced cartilage volume and increased risk of cartilage defects [Teichtahl *et al*. 2008; Wang *et al*. 2007]. Over 2 years, fat mass and percentage of fat mass were associated with an increased rate of patella cartilage volume loss [Teichtahl *et al*. 2009b].

In a cross-sectional sample of 190 randomly selected subjects, serum levels of leptin were negatively associated with tibial cartilage volume, and the association between body mass index and cartilage volume disappeared after adjustment for leptin [Ding *et al*. 2008]. These findings suggest that reduced cartilage volume associated with obesity is related to leptin and thus is hormonally mediated [Ding *et al*. 2008]. A longitudinal study of 172 randomly selected subjects showed baseline interleukin-6 predicted loss of tibial cartilage volume, independently of TNF-α, and that change in interleukin-6 and TNF-α was associated with increased loss of tibial cartilage volume, suggesting that low-level inflammation plays a role in the pathogenesis of knee OA [Stannus *et al*. 2010].

Physical activity

Whether physical activity is beneficial or detrimental to articular structures of weight-bearing joints is unclear. Although epidemiological studies on radiographic OA have yielded conflicting evidence, recent studies using MRI to assess articular cartilage have shown a beneficial effect of physical activity on joint health.

A beneficial effect of exercise was seen in adults at risk of OA who completed an exercise program three times a week over 4 months, showing increased glycosaminoglycan content in their knee cartilage using dGEMRIC [Roos and Dahlberg, 2005]. Increased cartilage volume was present and accrued over 2 years by children aged 9–18 years who participated in more vigorous sports [Jones *et al.* 2000, 2003]. Similarly, in healthy adults without clinical knee OA, vigorous activity is associated with increased cartilage volume and reduced prevalence of cartilage defects [Racunica *et al.* 2007], greater muscle strength and fitness endurance is associated with reduced cartilage volume loss [Foley *et al.* 2007]. Conversely, and providing further support for the benefits of physical activity on cartilage properties, adults who became quadriplegic have shown more rapid loss of knee cartilage thickness over 12 months compared to age- and gender-matched controls [Vanwanseele *et al.* 2002, 2003]. These data suggest that physical activity is required for cartilage development and maintenance at the knee.

In terms of longer-term exposure to physical activity, participation in vigorous physical activity has been shown to be associated with a reduced rate of patella cartilage volume loss in those with no significant patella cartilage defects at baseline, suggesting that vigorous physical activity is beneficial to patellofemoral joints for people without pre-existing cartilage damage [Teichtahl *et al.* 2009a].

Smoking

More recently, smoking has been shown to be a risk factor for structural progression in OA [Amin *et al.* 2007; Davies-Tuck *et al.* 2009; Ding *et al.* 2007a], with increased cartilage volume loss and cartilage defects in knee OA, particularly in current smokers [Amin *et al.* 2007; Ding *et al.* 2007a]. Smoking (current and former) also predicted increased cartilage volume loss over 2 years in a population without knee OA [Davies-Tuck *et al.* 2009]. The mechanism by which smoking affects structures in knee OA is unclear, although components of tobacco smoke affect chondrocyte function by inhibiting cell proliferation and extracellular matrix synthesis in the spine [Akmal *et al.* 2004; Uematsu *et al.* 2001]. Similar mechanisms may operate in the knee. The role of smoking in OA pathogenesis is complicated by interactions with other factors including genetics [Ding *et al.* 2007a] and bone marrow lesions [Davies-Tuck *et al.* 2009]. A gene–environment interaction was observed in one study where smoking influenced cartilage volume loss and cartilage defects primarily in the adult offspring of parents who had knee replacements for primary knee OA [Ding *et al.* 2007a]. Nevertheless, the mechanism by which smoking affects OA pathology warrants further investigation.

Vitamin D

Vitamin D affects cartilage by stimulating proteoglycan synthesis and has been shown to be beneficial to joint health [Boyan *et al.* 1997]. A MRI study of older adults showed baseline levels and change in serum levels of vitamin D were both positively associated with tibial cartilage volume, and vitamin D insufficiency predicted cartilage volume loss over 2.9 years [Ding *et al.* 2009].

Role of MRI cartilage parameters in assessing treatment response in OA

Recently it has been shown that MRI can be used as an outcome measure in intervention studies of OA, monitoring the response to treatment. A multicentre clinical trial comparing the effects of licofelone and naproxen on the progression of OA found that although cartilage volume loss was observed in both groups over time, the loss was significantly smaller in the group receiving licofelone [Raynauld *et al.* 2009]. In contrast, there was no significant change in joint space narrowing over that time [Raynauld *et al.* 2009]. Cartilage mean thickness loss was also significantly less in the licofelone compared with the naproxen group at 12 and 24 months [Raynauld *et al.* 2008]. In a multicentre, randomized, double-blind, controlled trial of 69 patients with knee OA and clinical signs of synovitis, patients receiving chondroitin sulphate had significantly less cartilage volume loss than the placebo group as early as 6 months for the global knee, lateral compartment, and tibial plateaus, with significance persisting at 12 months [Wildi *et al.* 2011]. In a randomized, double-blind, placebo-controlled clinical trial of 117 patients with knee OA, Wluka and colleagues found no effect of supplementary vitamin E on tibial cartilage volume loss over 2 years [Wluka *et al.* 2002a]. An open-label pilot study examined the potential of celecoxib compared with a modelized historical control cohort for disease-modifying effect in the treatment of knee OA [Raynauld *et al.* 2010]. Over 12 months, no effect of celecoxib on medial and lateral tibial cartilage volume loss was observed [Raynauld *et al.*

2010]. A recent randomized-controlled clinical trial found no effect of lateral wedge insoles worn for 12 months on medial tibial cartilage volume loss over the same time period [Bennell *et al*. 2011].

A recent study examining the effect of intra-articular hyaluronic acid injections on articular cartilage assessed by MRI detected significant difference in patellofemoral cartilage defects over 8 weeks in the hyaluronic acid group, but it was not significantly different compared with the control group receiving intra-articular saline injections [Cubukcu *et al*. 2005]. However, the small sample size and short time span of the study limited its ability to draw strong conclusion on the effect of intra-articular hyaluronic acid injections on articular cartilage. A recently published single-blind clinical trial found that patients with symptomatic knee OA receiving 6 monthly intra-articular injections of Hylan G-F 20 showed reduced cartilage volume loss and reduced progression of cartilage defects over 2 years when compared with those receiving usual care for knee OA [Wang *et al*. 2011].

A randomized, placebo-controlled, double-blind pilot trial of collagen hydrolysate for mild knee OA examined the short-term changes in knee hyaline cartilage assessed by dGEMRIC. This study found increased dGEMRIC score in the medial and lateral tibial regions of interest in participants assigned to collagen hydrolysate but decreased dGEMRIC score in the placebo arm, with the changes between the two groups at 24 weeks reaching significance, suggesting that the dGEMRIC technique may be able to detect change in proteoglycan content in knee cartilage within 24 weeks [McAlindon *et al*. 2011]. These studies demonstrated that the effect of intervention could be established earlier using MRI cartilage measures compared with radiology in clinical trials.

The use of MRI has the potential to optimize surgical management of knee pathology. A recent study of knees with anterior cruciate ligament injuries found significant differences in cartilage morphology (cartilage volume, cartilage thickness and cartilage surface area) in surgically treated knees compared with those without surgery [Frobell *et al*. 2009]. An anterior cruciate ligament reconstruction performed within a mean of 6 weeks from injury was associated with increased cartilage volume and cartilage thickness in the central medial femur and decreased cartilage surface area in the trochlea femur at 12 months, compared with knees treated without reconstruction [Frobell *et al*. 2009]. By using MRI to monitor cartilage morphologies postsurgery, the finding of the study suggest a delayed structural restitution in anterior cruciate ligament reconstructed knees, and that the timing of surgery may be important in minimizing adverse structural changes postsurgery. The study also suggests a possibility that surgically treated patients may require longer recovery period prior to rehabilitation since there is ongoing structural remodelling in the traumatic knee.

Conclusion

Although the focus of this review is on the role of MRI in assessing articular cartilage, it is clear that the real strength of MRI has been in its ability to assess the entire joint, including cartilage, subchondral bone, menisci, synovial tissue, and ligaments. OA has been recognized as a disease of the whole joint. Emerging evidence has suggested that subchondral bone expansion and lesions (bone marrow lesions, bone cysts, bone attrition) and meniscal pathologies (extrusion and tear) may predict cartilage loss and play a role in the pathogenesis of OA [Crema *et al*. 2010; Davies-Tuck *et al*. 2010; Ding *et al*. 2007b, 2007c; Hunter *et al*. 2006; Neogi *et al*. 2009; Tanamas *et al*. 2010]. Using radiographs to assess OA, a lot has been learned about the epidemiology of OA. However, it is clear that simply using radiographs is limited in assessing cartilage change as it is unable to detect early cartilage changes and it is insensitive to change. The use of MRI has allowed us to extend what has already been learned about the epidemiology of OA. Superior to radiographs, MRI modality allows accurate visualization of all joint components and is sensitive to longitudinal changes. Thus, we are able to determine the associations between modifiable factors and joint structures at an early stage and investigate the interrelationships among different joint structures, which have the potential for better understanding of the pathogenetic mechanisms in OA.

MRI has the potential to detect early cartilage changes, in particular, the changes in cartilage matrix composition at stages when cartilage damage is still reversible and treatable, although further research is needed to determine the validity, reproducibility, feasibility and clinical significance of these biomarkers in the assessment of early cartilage damage. MRI enables quantitative assessment of articular cartilage noninvasively, thus

representing a useful approach to determining the risk factors for OA, identifying the potential preventive strategies, monitoring the natural history of OA and evaluating the effect of therapeutic agents.

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The authors declare no conflicts of interest in preparing this article.

References

Adams, J.G., McAlindon, T., Dimasi, M., Carey, J. and Eustace, S. (1999) Contribution of meniscal extrusion and cartilage loss to joint space narrowing in osteoarthritis. *Clin Radiol* 54: 502–506.

Akella, S.V., Regatte, R.R., Gougoutas, A.J., Borthakur, A., Shapiro, E.M., Kneeland, J.B. *et al.* (2001) Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T. *Magn Reson Med* 46: 419–423.

Akmal, M., Kesani, A., Anand, B., Singh, A., Wiseman, M., Goodship, A. *et al.* (2004) Effect of nicotine on spinal disc cells: a cellular mechanism for disc degeneration. *Spine* 29: 568–575.

Altman, R., Brandt, K., Hochberg, M., Moskowitz, R., Bellamy, N., Bloch, D.A. *et al.* (1996) Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarthritis Cartilage* 4: 217–243.

Amin, S., LaValley, M.P., Guermazi, A., Grigoryan, M., Hunter, D.J., Clancy, M. *et al.* (2005) The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum* 52: 3152–3159.

Amin, S., Niu, J., Guermazi, A., Grigoryan, M., Hunter, D.J., Clancy, M. *et al.* (2007) Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Ann Rheum Dis* 66: 18–22.

Anandacoomarasamy, A., Smith, G., Leibman, S., Caterson, I., Giuffre, B., Fransen, M. *et al.* (2009) Cartilage defects are associated with physical disability in obese adults. *Rheumatology (Oxford)* 48: 1290–1293.

Bashir, A., Gray, M.L., Boutin, R.D. and Burstein, D. (1997) Glycosaminoglycan in articular cartilage: in vivo assessment with delayed Gd(DTPA) (2-)-enhanced MR imaging. *Radiology* 205: 551–558.

Bashir, A., Gray, M.L., Hartke, J. and Burstein, D. (1999) Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. *Magn Reson Med* 41: 857–865.

Bauer, J.S., Krause, S.J., Ross, C.J., Krug, R., Carballido-Gamio, J., Ozhinsky, E. *et al.* (2006) Volumetric cartilage measurements of porcine knee at 1.5-T and 3.0-T MR imaging: evaluation of precision and accuracy. *Radiology* 241: 399–406.

Bennell, K.L., Bowles, K.A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A. *et al.* (2011) Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *Bmj* 342: d2912.

Biswal, S., Hastie, T., Andriacchi, T.P., Bergman, G.A., Dillingham, M.F. and Lang, P. (2002) Risk factors for progressive cartilage loss in the knee: a longitudinal magnetic resonance imaging study in forty-three patients. *Arthritis Rheum* 46: 2884–2892.

Boegard, T., Rudling, O., Petersson, I.F. and Jonsson, K. (1998) Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. *Ann Rheum Dis* 57: 401–407.

Boyan, B.D., Posner, G.H., Greising, D.M., White, M.C., Sylvia, V.L., Dean, D.D. *et al.* (1997) Hybrid structural analogues of 1,25-(OH)2D3 regulate chondrocyte proliferation and proteoglycan production as well as protein kinase C through a nongenomic pathway. *J Cell Biochem* 66: 457–470.

Brandt, K.D., Fife, R.S., Braunstein, E.M. and Katz, B. (1991) Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. *Arthritis Rheum* 34: 1381–1386.

Bredella, M.A., Tirman, P.F., Peterfy, C.G., Zarlingo, M., Feller, J.F., Bost, F.W. *et al.* (1999) Accuracy of T2-weighted fast spin-echo MR imaging with fat saturation in detecting cartilage defects in the knee: comparison with arthroscopy in 130 patients. *AJR Am J Roentgenol* 172: 1073–1080.

Broderick, L.S., Turner, D.A., Renfrew, D.L., Schnitzer, T.J., Huff, J.P. and Harris, C. (1994) Severity of articular cartilage abnormality in patients with osteoarthritis: evaluation with fast spin-echo MR vs arthroscopy. *AJR Am J Roentgenol* 162: 99–103.

Bruyere, O., Genant, H., Kothari, M., Zaim, S., White, D., Peterfy, C. *et al.* (2007) Longitudinal study of magnetic resonance imaging and standard

X-rays to assess disease progression in osteoarthritis. *Osteoarthritis Cartilage* 15: 98–103.

Buckland-Wright, J.C., Macfarlane, D.G., Williams, S.A. and Ward, R.J. (1995) Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. *Ann Rheum Dis* 54: 872–880.

Buckwalter, J.A. and Mankin, H.J. (1998) Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr Course Lect* 47: 487–504.

Burgkart, R., Glaser, C., Hyhlik-Durr, A., Englmeier, K.H., Reiser, M. and Eckstein, F. (2001) Magnetic resonance imaging-based assessment of cartilage loss in severe osteoarthritis: accuracy, precision, and diagnostic value. *Arthritis Rheum* 44: 2072–2077.

Calabro, P. and Yeh, E.T. (2007) Obesity, inflammation, and vascular disease: the role of the adipose tissue as an endocrine organ. *Subcell Biochem* 42: 63–91.

Calvo, E., Palacios, I., Delgado, E., Ruiz-Cabello, J., Hernandez, P., Sanchez-Pernaute, O. *et al.* (2001) High-resolution MRI detects cartilage swelling at the early stages of experimental osteoarthritis. *Osteoarthritis Cartilage* 9: 463–472.

Calvo, E., Palacios, I., Delgado, E., Sanchez-Pernaute, O., Largo, R., Egido, J. *et al.* (2004) Histopathological correlation of cartilage swelling detected by magnetic resonance imaging in early experimental osteoarthritis. *Osteoarthritis Cartilage* 12: 878–886.

Caplan, A.I., Elyaderani, M., Mochizuki, Y., Wakitani, S. and Goldberg, V.M. (1997) Principles of cartilage repair and regeneration. *Clin Orthop* 342: 254–269.

Cicuttini, F., Forbes, A., Asbeutah, A., Morris, K. and Stuckey, S. (2000) Comparison and reproducibility of fast and conventional spoiled gradient-echo magnetic resonance sequences in the determination of knee cartilage volume. *J Orthop Res* 18: 580–584.

Cicuttini, F., Forbes, A., Morris, K., Darling, S., Bailey, M. and Stuckey, S. (1999) Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis Cartilage* 7: 265–271.

Cicuttini, F., Wluka, A., Wang, Y. and Stuckey, S. (2002a) The determinants of change in patella cartilage volume in osteoarthritic knees. *J Rheumatol* 29: 2615–2619.

Cicuttini, F.M., Forbes, A., Yuanyuan, W., Rush, G. and Stuckey, S.L. (2002b) Rate of knee cartilage loss after partial meniscectomy. *J Rheumatol* 29: 1954–1956.

Cicuttini, F.M., Jones, G., Forbes, A. and Wluka, A.E. (2004) Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. *Ann Rheum Dis* 63: 1124–1127.

Cicuttini, F.M., Teichtahl, A.J., Wluka, A.E., Davis, S., Strauss, B.J. and Ebeling, P.R. (2005) The relationship between body composition and knee cartilage volume in healthy, middle-aged subjects. *Arthritis Rheum* 52: 461–467.

Cicuttini, F.M., Wluka, A., Bailey, M., O'Sullivan, R., Poon, C., Yeung, S. *et al.* (2003a) Factors affecting knee cartilage volume in healthy men. *Rheumatology (Oxford)* 42: 258–262.

Cicuttini, F.M., Wluka, A.E., Forbes, A. and Wolfe, R. (2003b) Comparison of tibial cartilage volume and radiologic grade of the tibiofemoral joint. *Arthritis Rheum* 48: 682–688.

Cohen, Z.A., McCarthy, D.M., Kwak, S.D., Legrand, P., Fogarasi, F., Ciaccio, E.J. *et al.* (1999) Knee cartilage topography, thickness, and contact areas from MRI: in-vitro calibration and in-vivo measurements. *Osteoarthritis Cartilage* 7: 95–109.

Crema, M.D., Guermazi, A., Li, L., Nogueira-Barbosa, M.H., Marra, M.D., Roemer, F.W. *et al.* (2010) The association of prevalent medial meniscal pathology with cartilage loss in the medial tibiofemoral compartment over a 2-year period. *Osteoarthritis Cartilage* 18: 336–343.

Cubukcu, D., Ardic, F., Karabulut, N. and Topuz, O. (2005) Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment. *Clin Rheumatol* 24: 336-341.

Davies-Tuck, M., Wluka, A.E., Forbes, A., Wang, Y., English, D.R., Giles, G.G. *et al.* (2010) Development of bone marrow lesions is associated with adverse effects on knee cartilage while resolution is associated with improvement - a potential target for prevention of knee osteoarthritis: a longitudinal study. *Arthritis Res Ther* 12(1): R10.

Davies-Tuck, M.L., Wluka, A.E., Forbes, A., Wang, Y., English, D.R., Giles, G.G. *et al.* (2009) Smoking is associated with increased cartilage loss and persistence of bone marrow lesions over 2 years in community-based individuals. *Rheumatology* 48: 1227–1231.

Davies-Tuck, M.L., Wluka, A.E., Wang, Y., Teichtahl, A.J., Jones, G., Ding, C. *et al.* (2008) The natural history of cartilage defects in people with knee osteoarthritis. *Osteoarthritis Cartilage* 16: 337–342.

Ding, C., Cicuttini, F., Blizzard, L., Jones, G., Ding, C., Cicuttini, F. *et al.* (2007a) Smoking interacts with family history with regard to change in knee cartilage volume and cartilage defect development. *Arthritis Rheum* 56: 1521–1528.

Ding, C., Cicuttini, F. and Jones, G. (2007b) Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis. *Osteoarthritis Cartilage* 15: 479–486.

Ding, C., Cicuttini, F., Parameswaran, V., Burgess, J., Quinn, S. and Jones, G. (2009) Serum levels of vitamin D, sunlight exposure, and knee cartilage loss in older adults: The Tasmanian older adult cohort study. *Arthritis Rheum* 60: 1381–1389.

Ding, C., Cicuttini, F., Scott, F., Boon, C. and Jones, G. (2005a) Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. *Arthritis Rheum* 52: 3918–3927.

Ding, C., Cicuttini, F., Scott, F., Cooley, H., Boon, C. and Jones, G. (2006) Natural history of knee cartilage defects and factors affecting change. *Arch Intern Med* 166: 651–658.

Ding, C., Cicuttini, F., Scott, F., Cooley, H. and Jones, G. (2005b) Knee Structural Alteration and BMI: A Cross-sectional Study. *Obes Res* 13: 350–361.

Ding, C., Cicuttini, F., Scott, F., Glisson, M. and Jones, G. (2003) Sex differences in knee cartilage volume in adults: role of body and bone size, age and physical activity. *Rheumatology (Oxford)* 42: 1317–1323.

Ding, C., Garnero, P., Cicuttini, F., Scott, F., Cooley, H. and Jones, G. (2005c) Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. *Osteoarthritis Cartilage* 13: 198–205.

Ding, C., Martel-Pelletier, J., Pelletier, J.P., Abram, F., Raynauld, J.P., Cicuttini, F. *et al.* (2007c) Knee meniscal extrusion in a largely non-osteoarthritic cohort: association with greater loss of cartilage volume. *Arthritis Res Ther* 9(2): R21.

Ding, C., Parameswaran, V., Cicuttini, F., Burgess, J., Zhai, G., Quinn, S. *et al.* (2008) Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. *Ann Rheum Dis* 67: 1256–1261.

Disler, D.G., McCauley, T.R., Kelman, C.G., Fuchs, M.D., Ratner, L.M., Wirth, C.R. *et al.* (1996) Fat-suppressed three-dimensional spoiled gradient-echo MR imaging of hyaline cartilage defects in the knee: comparison with standard MR imaging and arthroscopy. *AJR Am J Roentgenol* 167: 127–132.

Duc, S.R., Pfirrmann, C.W., Koch, P.P., Zanetti, M. and Hodler, J. (2008) Internal knee derangement assessed with 3-minute three-dimensional isovoxel true FISP MR sequence: preliminary study. *Radiology* 246: 526–535.

Duc, S.R., Pfirrmann, C.W., Schmid, M.R., Zanetti, M., Koch, P.P., Kalberer, F. *et al.* (2007) Articular cartilage defects detected with 3D water-excitation true FISP: prospective comparison with sequences commonly used for knee imaging. *Radiology* 245: 216–223.

Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., Netter, P. *et al.* (2003) Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 48: 3118–3129.

Dunn, T.C., Lu, Y., Jin, H., Ries, M.D. and Majumdar, S. (2004) T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. *Radiology* 232: 592–598.

Dupuy, D.E., Spillane, R.M., Rosol, M.S., Rosenthal, D.I., Palmer, W.E., Burke, D.W. *et al.* (1996) Quantification of articular cartilage in the knee with three-dimensional MR imaging. *Acad Radiol* 3: 919–924.

Duvvuri, U., Kudchodkar, S., Reddy, R. and Leigh, J.S. (2002) T(1rho) relaxation can assess longitudinal proteoglycan loss from articular cartilage in vitro. *Osteoarthritis Cartilage* 10: 838-844.

Eckstein, F., Adam, C., Sittek, H., Becker, C., Milz, S., Schulte, E. *et al.* (1997) Non-invasive determination of cartilage thickness throughout joint surfaces using magnetic resonance imaging. *J Biomech* 30: 285–289.

Eckstein, F., Charles, H.C., Buck, R.J., Kraus, V.B., Remmers, A.E., Hudelmaier, M. *et al.* (2005) Accuracy and precision of quantitative assessment of cartilage morphology by magnetic resonance imaging at 3.0T. *Arthritis Rheum* 52: 3132–3136.

Eckstein, F., Cicuttini, F., Raynauld, J.P., Waterton, J.C. and Peterfy, C. (2006) Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. *Osteoarthritis Cartilage* 14(Suppl. A): A46–A75.

Eckstein, F., Cotofana, S., Wirth, W., Nevitt, M., John, M.R., Dreher, D. *et al.* (2011) Greater rates of cartilage loss in painful knees than in pain-free knees after adjustment for radiographic disease stage: Data from the osteoarthritis initiative. *Arthritis Rheum* 63: 2257–2267.

Eckstein, F., Gavazzeni, A., Sittek, H., Haubner, M., Losch, A., Milz, S. *et al.* (1996) Determination of knee joint cartilage thickness using three-dimensional magnetic resonance chondro-crassometry (3D MR-CCM). *Magn Reson Med* 36: 256–265.

Eckstein, F., Heudorfer, L., Faber, S.C., Burgkart, R., Englmeier, K.H. and Reiser, M. (2002) Long-term and resegmentation precision of quantitative cartilage MR imaging (qMRI). *Osteoarthritis Cartilage* 10: 922–928.

Eckstein, F., Maschek, S., Wirth, W., Hudelmaier, M., Hitzl, W., Wyman, B. *et al.* (2009) One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. *Ann Rheum Dis* 68: 674–679.

Eckstein, F., Schnier, M., Haubner, M., Priebsch, J., Glaser, C., Englmeier, K.H. *et al.* (1998a) Accuracy of cartilage volume and thickness measurements with magnetic resonance imaging. *Clin Orthop* 352: 137–148.

Eckstein, F., Westhoff, J., Sittek, H., Maag, K.P., Haubner, M., Faber, S. *et al.* (1998b) In vivo reproducibility of three-dimensional cartilage volume and thickness measurements with MR imaging. *AJR Am J Roentgenol* 170: 593–597.

Eckstein, F., Wirth, W., Hudelmaier, M., Stein, V., Lengfelder, V., Cahue, S. *et al.* (2008) Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. *Arthritis Rheum* 59: 1563–1570.

Evans, C.H. (2005) Novel biological approaches to the intra-articular treatment of osteoarthritis. *BioDrugs* 19: 355–362.

Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M. *et al.* (2000) Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 133: 635–646.

Figenschau, Y., Knutsen, G., Shahazeydi, S., Johansen, O. and Sveinbjornsson, B. (2001) Human articular chondrocytes express functional leptin receptors. *Biochem Biophys Res Commun* 287: 190–197.

Fischbach, F., Bruhn, H., Unterhauser, F., Ricke, J., Wieners, G., Felix, R. *et al.* (2005) Magnetic resonance imaging of hyaline cartilage defects at 1.5T and 3.0T: comparison of medium T2-weighted fast spin echo, T1-weighted two-dimensional and three-dimensional gradient echo pulse sequences. *Acta Radiol* 46: 67–73.

Foley, S., Ding, C., Cicuttini, F. and Jones, G. (2007) Physical activity and knee structural change: a longitudinal study using MRI. *Med Sci Sports Exerc* 39: 426–434.

Frobell, R.B. (2011) Change in cartilage thickness, posttraumatic bone marrow lesions, and joint fluid volumes after acute ACL disruption: a two-year prospective MRI study of sixty-one subjects. *J Bone Joint Surg Am* 93: 1096–1103.

Frobell, R.B., Le Graverand, M.P., Buck, R., Roos, E.M., Roos, H.P., Tamez-Pena, J. *et al.* (2009) The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. *Osteoarthritis Cartilage* 17: 161–167.

Gale, D.R., Chaisson, C.E., Totterman, S.M., Schwartz, R.K., Gale, M.E. and Felson, D. (1999) Meniscal subluxation: association with osteoarthritis and joint space narrowing. *Osteoarthritis Cartilage* 7: 526–532.

Gandy, S.J., Dieppe, P.A., Keen, M.C., Maciewicz, R.A., Watt, I. and Waterton, J.C. (2002) No loss of cartilage volume over three years in patients with knee osteoarthritis as assessed by magnetic resonance imaging. *Osteoarthritis Cartilage* 10: 929–937.

Graichen, H., von Eisenhart-Rothe, R., Vogl, T., Englmeier, K.H. and Eckstein, F. (2004) Quantitative assessment of cartilage status in osteoarthritis by quantitative magnetic resonance imaging: technical validation for use in analysis of cartilage volume and further morphologic parameters. *Arthritis Rheum* 50: 811–816.

Hanna, F., Ebeling, P.R., Wang, Y., O'Sullivan, R., Davis, S., Wluka, A.E. *et al.* (2005) Factors influencing longitudinal change in knee cartilage volume measured from magnetic resonance imaging in healthy men. *Ann Rheum Dis* 64: 1038–1042.

Hanna, F.S., Bell, R.J., Davis, S.R., Wluka, A.E., Teichtahl, A.J., O'Sullivan, R. *et al.* (2007) Factors affecting patella cartilage and bone in middle-aged women. *Arthritis Rheum* 57: 272–278.

Hayashi, D., Roemer, F.W. and Guermazi, A. (2010) Choice of pulse sequences for magnetic resonance imaging-based semiquantitative assessment of cartilage defects in osteoarthritis research: Comment on the article by Dore et al. *Arthritis Rheum* 62: 3830–3831.

Hudelmaier, M., Glaser, C., Englmeier, K.H., Reiser, M., Putz, R., Eckstein, F. *et al.* (2003) Correlation of knee-joint cartilage morphology with muscle cross-sectional areas vs. anthropometric variables. *Anatomical Record Part A, Discoveries in Mol Cell Evol Biol* 270: 175–184.

Hudelmaier, M., Glaser, C., Hohe, J., Englmeier, K.H., Reiser, M., Putz, R. *et al.* (2001) Age-related changes in the morphology and deformational behavior of knee joint cartilage. *Arthritis Rheum* 44: 2556–2561.

Hudelmaier, M., Wirth, W., Wehr, B., Kraus, V., Wyman, B.T., Hellio Le Graverand, M.P. *et al.* (2010) Femorotibial cartilage morphology: reproducibility of different metrics and femoral regions, and sensitivity to change in disease. *Cells Tissues Organs* 192: 340–350.

Hunter, D.J., March, L. and Sambrook, P.N. (2003) The association of cartilage volume with knee pain. *Osteoarthritis Cartilage* 11: 725–729.

Hunter, D.J., Niu, J., Zhang, Y., Totterman, S., Tamez, J., Dabrowski, C. *et al.* (2009) Change in cartilage morphometry: a sample of the progression

cohort of the Osteoarthritis Initiative. *Ann Rheum Dis* 68: 349–356.

Hunter, D.J., Zhang, Y., Niu, J., Goggins, J., Amin, S., LaValley, M.P. *et al.* (2006) Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum* 54: 1529–1535.

Jones, G., Ding, C., Glisson, M., Hynes, K., Ma, D. and Cicuttini, F. (2003) Knee articular cartilage development in children: a longitudinal study of the effect of sex, growth, body composition, and physical activity. *Pediatr Res* 54: 230–236.

Jones, G., Ding, C., Scott, F., Glisson, M. and Cicuttini, F. (2004) Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. *Osteoarthritis Cartilage* 12: 169–174.

Jones, G., Glisson, M., Hynes, K. and Cicuttini, F. (2000) Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. *Arthritis Rheum* 43: 2543–2549.

Karvonen, R.L., Negendank, W.G., Fraser, S.M., Mayes, M.D., An, T. and Fernandez-Madrid, F. (1990) Articular cartilage defects of the knee: correlation between magnetic resonance imaging and gross pathology. *Ann Rheum Dis* 49: 672–675.

Karvonen, R.L., Negendank, W.G., Teitge, R.A., Reed, A.H., Miller, P.R. and Fernandez-Madrid, F. (1994) Factors affecting articular cartilage thickness in osteoarthritis and aging. *J Rheumatol* 21: 1310–1318.

Kawahara, Y., Uetani, M., Nakahara, N., Doiguchi, Y., Nishiguchi, M., Futagawa, S. *et al.* (1998) Fast spin-echo MR of the articular cartilage in the osteoarthrotic knee. Correlation of MR and arthroscopic findings. *Acta Radiol* 39: 120–125.

Kijowski, R., Blankenbaker, D.G., Davis, K.W., Shinki, K., Kaplan, L.D. and De Smet, A.A. (2009) Comparison of 1.5- and 3.0-T MR imaging for evaluating the articular cartilage of the knee joint. *Radiology* 250: 839–848.

Kijowski, R., Blankenbaker, D.G., Woods, M.A., Shinki, K., De Smet, A.A. and Reeder, S.B. (2010) 3.0-T evaluation of knee cartilage by using three-dimensional IDEAL GRASS imaging: comparison with fast spin-echo imaging. *Radiology* 255: 117–127.

Kim, S.J., Ju, J.W., Oh, C.D., Yoon, Y.M., Song, W.K., Kim, J.H. *et al.* (2002) ERK-1/2 and p38 kinase oppositely regulate nitric oxide-induced apoptosis of chondrocytes in association with p53, caspase-3, and differentiation status. *J Biol Chem* 277: 1332–1339.

Kladny, B., Bail, H., Swoboda, B., Schiwy-Bochat, H., Beyer, W.F. and Weseloh, G. (1996) Cartilage thickness measurement in magnetic resonance imaging. *Osteoarthritis Cartilage* 4: 181–186.

Koff, M.F., Amrami, K.K. and Kaufman, K.R. (2007) Clinical evaluation of T2 values of patellar cartilage in patients with osteoarthritis. *Osteoarthritis Cartilage* 15: 198–204.

Koo, S., Gold, G.E. and Andriacchi, T.P. (2005) Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. *Osteoarthritis Cartilage* 13: 782–789.

Kornaat, P.R., Ceulemans, R.Y., Kroon, H.M., Riyazi, N., Kloppenburg, M., Carter, W.O. *et al.* (2005a) MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)—inter-observer and intra-observer reproducibility of a compartment-based scoring system. *Skeletal Radiol* 34: 95–102.

Kornaat, P.R., Reeder, S.B., Koo, S., Brittain, J.H., Yu, H., Andriacchi, T.P. *et al.* (2005b) MR imaging of articular cartilage at 1.5T and 3.0T: comparison of SPGR and SSFP sequences. *Osteoarthritis Cartilage* 13: 338–344.

Kraus, V.B., Feng, S., Wang, S., White, S., Ainslie, M., Brett, A. *et al.* (2009) Trabecular morphometry by fractal signature analysis is a novel marker of osteoarthritis progression. *Arthritis Rheum* 60: 3711–3722.

Kshirsagar, A.A., Watson, P.J., Tyler, J.A. and Hall, L.D. (1998) Measurement of localized cartilage volume and thickness of human knee joints by computer analysis of three-dimensional magnetic resonance images. *Invest Radiol* 33: 289–299.

Li, X., Han, E.T., Ma, C.B., Link, T.M., Newitt, D.C. and Majumdar, S. (2005) In vivo 3T spiral imaging based multi-slice T(1rho) mapping of knee cartilage in osteoarthritis. *Magn Reson Med* 54: 929–936.

Li, X., Kuo, D., Theologis, A., Carballido-Gamio, J., Stehling, C., Link, T.M. *et al.* (2011) Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2—initial experience with 1-year follow-up. *Radiology* 258: 505–514.

Liess, C., Lusse, S., Karger, N., Heller, M. and Gluer, C.C. (2002) Detection of changes in cartilage water content using MRI T2-mapping in vivo. *Osteoarthritis Cartilage* 10: 907–913.

Link, T.M., Sell, C.A., Masi, J.N., Phan, C., Newitt, D., Lu, Y. *et al.* (2006) 3.0 vs 1.5 T MRI in the detection of focal cartilage pathology—ROC analysis in an experimental model. *Osteoarthritis Cartilage* 14: 63–70.

Link, T.M., Stahl, R. and Woertler, K. (2007) Cartilage imaging: motivation, techniques, current and future significance. *Eur Radiol* 17: 1135-1146.

Link, T.M., Steinbach, L.S., Ghosh, S., Ries, M., Lu, Y., Lane, N. *et al.* (2003) Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 226: 373–381.

Malemud, C.J. (2004) Cytokines as therapeutic targets for osteoarthritis. *BioDrugs* 18: 23-35.

Marshall, K.W., Guthrie, B.T. and Mikulis, D.J. (1995a) Quantitative cartilage imaging. *Br J Rheumatol* 34(Suppl. 1): 29–31.

Marshall, K.W., Mikulis, D.J. and Guthrie, B.M. (1995b) Quantitation of articular cartilage using magnetic resonance imaging and three-dimensional reconstruction. *J Orthop Res* 13: 814–823.

Masi, J.N., Sell, C.A., Phan, C., Han, E., Newitt, D., Steinbach, L. *et al.* (2005) Cartilage MR imaging at 3.0 *versus* that at 1.5 T: preliminary results in a porcine model. *Radiology* 236: 140–150.

McAlindon, T.E., Nuite, M., Krishnan, N., Ruthazer, R., Price, L.L., Burstein, D. *et al.* (2011) Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. *Osteoarthritis Cartilage* 19: 399–405.

McGibbon, C.A. and Trahan, C.A. (2003) Measurement accuracy of focal cartilage defects from MRI and correlation of MRI graded lesions with histology: a preliminary study. *Osteoarthritis Cartilage* 11: 483–493.

Mohr, A., Priebe, M., Taouli, B., Grimm, J., Heller, M. and Brossmann, J. (2003) Selective water excitation for faster MR imaging of articular cartilage defects: initial clinical results. *Eur Radiol* 13: 686–689.

Mosher, T.J., Dardzinski, B.J. and Smith, M.B. (2000) Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2--preliminary findings at 3 T. *Radiology* 214: 259–266.

Murphy, B.J. (2001) Evaluation of grades 3 and 4 chondromalacia of the knee using T2*-weighted 3D gradient-echo articular cartilage imaging. *Skeletal Radiol* 30: 305–311.

Neogi, T., Felson, D., Niu, J., Lynch, J., Nevitt, M., Guermazi, A. *et al.* (2009) Cartilage loss occurs in the same subregions as subchondral bone attrition: A within-knee subregion-matched approach from the multicenter osteoarthritis study. *Arthritis Rheum* 61: 1539–1544.

Nishimura, K., Tanabe, T., Kimura, M., Harasawa, A., Karita, K. and Matsushita, T. (2005) Measurement of articular cartilage volumes in the normal knee by magnetic resonance imaging: can cartilage volumes be estimated from physical characteristics? *J Orthop Sci* 10: 246–252.

Otero, M., Gomez Reino, J.J. and Gualillo, O. (2003) Synergistic induction of nitric oxide synthase type II: in vitro effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells. *Arthritis Rheum* 48: 404–409.

Owman, H., Tiderius, C.J., Neuman, P., Nyquist, F. and Dahlberg, L.E. (2008) Association between findings on delayed gadolinium-enhanced magnetic resonance imaging of cartilage and future knee osteoarthritis. *Arthritis Rheum* 58: 1727–1730.

Pakin, S.K., Schweitzer, M.E. and Regatte, R.R. (2006) 3D-T1rho quantitation of patellar cartilage at 3.0T. *J Magn Reson Imaging* 24: 1357–1363.

Pelletier, J.P., Raynauld, J.P., Berthiaume, M.J., Abram, F., Choquette, D., Haraoui, B. *et al.* (2007) Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. *Arthritis Res Ther* 9(4): R74.

Peterfy, C.G., Guermazi, A., Zaim, S., Tirman, P.F., Miaux, Y., White, D. *et al.* (2004) Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage* 12: 177–190.

Peterfy, C.G., van Dijke, C.F., Janzen, D.L., Gluer, C.C., Namba, R., Majumdar, S. *et al.* (1994) Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: optimization and validation. *Radiology* 192: 485–491.

Phan, C.M., Link, T.M., Blumenkrantz, G., Dunn, T.C., Ries, M.D., Steinbach, L.S. *et al.* (2006) MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. *Eur Radiol* 16: 608–618.

Pilch, L., Stewart, C., Gordon, D., Inman, R., Parsons, K., Pataki, I. *et al.* (1994) Assessment of cartilage volume in the femorotibial joint with magnetic resonance imaging and 3D computer reconstruction. *J Rheumatol* 21: 2307–2321.

Piplani, M.A., Disler, D.G., McCauley, T.R., Holmes, T.J. and Cousins, J.P. (1996) Articular cartilage volume in the knee: semiautomated determination from three-dimensional reformations of MR images. *Radiology* 198: 855–859.

Pottie, P., Presle, N., Terlain, B., Netter, P., Mainard, D. and Berenbaum, F. (2006) Obesity and osteoarthritis: more complex than predicted! *Ann Rheum Dis* 65: 1403–1405.

Racunica, T.L., Teichtahl, A.J., Wang, Y., Wluka, A.E., English, D.R., Giles, G.G. *et al.* (2007) Effect of physical activity on articular knee joint structures in community-based adults. *Arthritis Rheum* 57: 1261–1268.

Ravaud, P., Auleley, G.R., Chastang, C., Rousselin, B., Paolozzi, L., Amor, B. *et al.* (1996) Knee joint space width measurement: an experimental study of the influence of radiographic procedure and joint positioning. *Br J Rheumatol* 35: 761–766.

Raynauld, J.P., Kauffmann, C., Beaudoin, G., Berthiaume, M.J., de Guise, J.A., Bloch, D.A. *et al.* (2003) Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. *Osteoarthritis Cartilage* 11: 351–360.

Raynauld, J.P., Martel-Pelletier, J., Abram, F., Dorais, M., Haraoui, B., Choquette, D. *et al.* (2008) Analysis of the precision and sensitivity to change of different approaches to assess cartilage loss by quantitative MRI in a longitudinal multicentre clinical trial in patients with knee osteoarthritis. *Arthritis Res Ther* 10(6): R129.

Raynauld, J.P., Martel-Pelletier, J., Beaulieu, A., Bessette, L., Morin, F., Choquette, D. *et al.* (2010) An open-label pilot study evaluating by magnetic resonance imaging the potential for a disease-modifying effect of celecoxib compared to a modelized historical control cohort in the treatment of knee osteoarthritis. *Semin Arthritis Rheum* 40: 185–192.

Raynauld, J.P., Martel-Pelletier, J., Berthiaume, M.J., Beaudoin, G., Choquette, D., Haraoui, B. *et al.* (2006) Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. *Arthritis Res Ther* 8(1): R21.

Raynauld, J.P., Martel-Pelletier, J., Berthiaume, M.J., Labonte, F., Beaudoin, G., de Guise, J.A. *et al.* (2004) Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum* 50: 476–487.

Raynauld, J.P., Martel-Pelletier, J., Bias, P., Laufer, S., Haraoui, B., Choquette, D. *et al.* (2009) Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, *versus* naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis* 68: 938–947.

Recht, M.P., Piraino, D.W., Paletta, G.A., Schils, J.P. and Belhobek, G.H. (1996) Accuracy of fat-suppressed three-dimensional spoiled gradient-echo FLASH MR imaging in the detection of patellofemoral articular cartilage abnormalities. *Radiology* 198: 209–212.

Regatte, R.R., Akella, S.V., Borthakur, A., Kneeland, J.B. and Reddy, R. (2002) Proteoglycan depletion-induced changes in transverse relaxation maps of cartilage: comparison of T2 and T1rho. *Acad Radiol* 9: 1388–1394.

Regatte, R.R., Akella, S.V., Borthakur, A. and Reddy, R. (2003) Proton spin-lock ratio imaging for quantitation of glycosaminoglycans in articular cartilage. *J Magn Reson Imaging* 17: 114–121.

Regatte, R.R., Akella, S.V., Lonner, J.H., Kneeland, J.B. and Reddy, R. (2006) T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. *J Magn Reson Imaging* 23: 547–553.

Regatte, R.R., Akella, S.V., Wheaton, A.J., Lech, G., Borthakur, A., Kneeland, J.B. *et al.* (2004) 3D-T1rho-relaxation mapping of articular cartilage: in vivo assessment of early degenerative changes in symptomatic osteoarthritic subjects. *Acad Radiol* 11: 741–749.

Roemer, F.W., Eckstein, F. and Guermazi, A. (2009) Magnetic resonance imaging-based semiquantitative and quantitative assessment in osteoarthritis. *Rheum Dis Clin North Am* 35: 521–555.

Roos, E.M. and Dahlberg, L. (2005) Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum* 52: 3507–3514.

Roubenoff, R. (1996) Applications of bioelectrical impedance analysis for body composition to epidemiologic studies. *Am J Clin Nutr* 64(3 Suppl.): 459S–462S.

Sharma, L., Eckstein, F., Song, J., Guermazi, A., Prasad, P., Kapoor, D. *et al.* (2008) Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. *Arthritis Rheum* 58: 1716–1726.

Sittek, H., Eckstein, F., Gavazzeni, A., Milz, S., Kiefer, B., Schulte, E. *et al.* (1996) Assessment of normal patellar cartilage volume and thickness using MRI: an analysis of currently available pulse sequences. *Skeletal Radiol* 25: 55–62.

Sowers, M.F., Hayes, C., Jamadar, D., Capul, D., Lachance, L., Jannausch, M. *et al.* (2003) Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis. *Osteoarthritis Cartilage* 11(6): 387–393.

Stahl, R., Blumenkrantz, G., Carballido-Gamio, J., Zhao, S., Munoz, T., Hellio Le Graverand-Gastineau, M.P. *et al.* (2007) MRI-derived T2 relaxation times

and cartilage morphometry of the tibio-femoral joint in subjects with and without osteoarthritis during a 1-year follow-up. *Osteoarthritis Cartilage* 15: 1225–1234.

Stahl, R., Luke, A., Li, X., Carballido-Gamio, J., Ma, C.B., Majumdar, S. *et al.* (2009) T1rho, T2 and focal knee cartilage abnormalities in physically active and sedentary healthy subjects *versus* early OA patients—a 3.0-Tesla MRI study. *Eur Radiol* 19: 132–143.

Stannus, O., Jones, G., Cicuttini, F., Parameswaran, V., Quinn, S., Burgess, J. *et al.* (2010) Circulating levels of IL-6 and TNF-alpha are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. *Osteoarthritis Cartilage* 18: 1441–1447.

Tanamas, S.K., Wluka, A.E., Pelletier, J.P., Martel-Pelletier, J., Abram, F., Wang, Y. *et al.* (2010) The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study. *Arthritis Res Ther* 12(2): R58.

Teichtahl, A.J., Wang, Y., Wluka, A.E., Szramka, M., English, D.R., Giles, G.G. *et al.* (2008) The longitudinal relationship between body composition and patella cartilage in healthy adults. *Obesity (Silver Spring)* 16: 421–427.

Teichtahl, A.J., Wluka, A.E., Forbes, A., Wang, Y., English, D.R., Giles, G.G. *et al.* (2009a) Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. *Arthritis Rheum* 61: 1095–1102.

Teichtahl, A.J., Wluka, A.E., Wang, Y., Hanna, F., English, D.R., Giles, G.G. *et al.* (2009b) Obesity and adiposity are associated with the rate of patella cartilage volume loss over 2 years in adults without knee osteoarthritis. *Ann Rheum Dis* 68: 909–913.

Trattnig, S., Mlynarik, V., Breitenseher, M., Huber, M., Zembsch, A., Rand, T. *et al.* (1999) MRI visualization of proteoglycan depletion in articular cartilage via intravenous administration of Gd-DTPA. *Magn Reson Imaging* 17: 577–583.

Uematsu, Y., Matuzaki, H. and Iwahashi, M. (2001) Effects of nicotine on the intervertebral disc: an experimental study in rabbits. *J Orthopaedic Sci* 6: 177–182.

Vanwanseele, B., Eckstein, F., Knecht, H., Spaepen, A. and Stussi, E. (2003) Longitudinal analysis of cartilage atrophy in the knees of patients with spinal cord injury. *Arthritis Rheum* 48: 3377–3381.

Vanwanseele, B., Eckstein, F., Knecht, H., Stussi, E. and Spaepen, A. (2002) Knee cartilage of spinal cord-injured patients displays progressive thinning in the absence of normal joint loading and movement. *Arthritis Rheum* 46: 2073–2078.

Wang, Y., Ding, C., Wluka, A.E., Davis, S., Ebeling, P.R., Jones, G. *et al.* (2006) Factors affecting progression of knee cartilage defects in normal subjects over 2 years. *Rheumatology (Oxford)* 45: 79–84.

Wang, Y., Hall, S., Hanna, F., Wluka, A.E., Grant, G., Marks, P. *et al.* (2011) Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC Musculoskelet Disord* 12: 195.

Wang, Y., Wluka, A.E., English, D.R., Teichtahl, A.J., Giles, G.G., O'Sullivan, R. *et al.* (2007) Body composition and knee cartilage properties in healthy, community-based adults. *Ann Rheum Dis* 99: 1244–1248.

Watson, P.J., Carpenter, T.A., Hall, L.D. and Tyler, J.A. (1996) Cartilage swelling and loss in a spontaneous model of osteoarthritis visualized by magnetic resonance imaging. *Osteoarthritis Cartilage* 4: 197–207.

Wheaton, A.J., Casey, F.L., Gougoutas, A.J., Dodge, G.R., Borthakur, A., Lonner, J.H. *et al.* (2004) Correlation of T1rho with fixed charge density in cartilage. *J Magn Reson Imaging* 20: 519–525.

Wheaton, A.J., Dodge, G.R., Elliott, D.M., Nicoll, S.B. and Reddy, R. (2005) Quantification of cartilage biomechanical and biochemical properties via T1rho magnetic resonance imaging. *Magn Reson Med* 54: 1087–1093.

Wildi, L.M., Raynauld, J.P., Martel-Pelletier, J., Beaulieu, A., Bessette, L., Morin, F. *et al.* (2011) Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis* 70: 982–989.

Williams, A., Sharma, L., McKenzie, C.A., Prasad, P.V. and Burstein, D. (2005) Delayed gadolinium-enhanced magnetic resonance imaging of cartilage in knee osteoarthritis: findings at different radiographic stages of disease and relationship to malalignment. *Arthritis Rheum* 52: 3528–3535.

Wirth, W., Hellio Le Graverand, M.P., Wyman, B.T., Maschek, S., Hudelmaier, M., Hitzl, W. *et al.* (2009) Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. *Osteoarthritis Cartilage* 17: 291–297.

Wirth, W., Larroque, S., Davies, R.Y., Nevitt, M., Gimona, A., Baribaud, F. *et al.* (2011) Comparison of 1-year vs 2-year change in regional cartilage thickness in osteoarthritis results from 346 participants from

the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 19: 74–83.

Wluka, A.E., Ding, C., Jones, G. and Cicuttini, F.M. (2005) The clinical correlates of articular cartilage defects in symptomatic knee osteoarthritis: a prospective study. *Rheumatology* 44: 1311–1316.

Wluka, A.E., Stuckey, S., Brand, C. and Cicuttini, F.M. (2002a) Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. *J Rheumatol* 29: 2585–2591.

Wluka, A.E., Stuckey, S., Snaddon, J. and Cicuttini, F.M. (2002b) The determinants of change in tibial cartilage volume in osteoarthritic knees. *Arthritis Rheum* 46: 2065–2072.

Wluka, A.E., Wolfe, R., Davis, S.R., Stuckey, S. and Cicuttini, F.M. (2004a) Tibial cartilage volume change in healthy postmenopausal women: a longitudinal study. *Ann Rheum Dis* 63: 444–449.

Wluka, A.E., Wolfe, R., Stuckey, S. and Cicuttini, F.M. (2004b) How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? *Ann Rheum Dis* 63: 264–268.

Woertler, K., Strothmann, M., Tombach, B. and Reimer, P. (2000) Detection of articular cartilage lesions: experimental evaluation of low- and high-field-strength MR imaging at 0.18 and 1.0 T. *J Magn Reson Imaging* 11: 678–685.

Wolski, M., Podsiadlo, P., Stachowiak, G.W., Lohmander, L.S. and Englund, M. (2010) Differences in trabecular bone texture between knees with and without radiographic osteoarthritis detected by directional fractal signature method. *Osteoarthritis Cartilage* 18: 684–690.

Wolski, M., Stachowiak, G.W., Dempsey, A.R., Mills, P.M., Cicuttini, F.M., Wang, Y. *et al.* (2011) Trabecular bone texture detected by plain radiography and variance orientation transform method is different between knees with and without cartilage defects. *J Orthop Res* 29: 1161–1167.

Wong, S., Steinbach, L., Zhao, J., Stehling, C., Ma, C.B. and Link, T.M. (2009) Comparative study of imaging at 3.0 T *versus*1.5 T of the knee. *Skeletal Radiol* 38: 761–769.

Yoshioka, H., Stevens, K., Hargreaves, B.A., Steines, D., Genovese, M., Dillingham, M.F. *et al.* (2004) Magnetic resonance imaging of articular cartilage of the knee: comparison between fat-suppressed three-dimensional SPGR imaging, fat-suppressed FSE imaging, and fat-suppressed three-dimensional DEFT imaging, and correlation with arthroscopy. *J Magn Reson Imaging* 20: 857–864.

Zhai, G., Blizzard, L., Srikanth, V., Ding, C., Cooley, H., Cicuttini, F. *et al.* (2006) Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. *Arthritis Rheum* 55: 264–271.

Zhai, G., Cicuttini, F., Ding, C., Scott, F., Garnero, P. and Jones, G. (2007) Correlates of knee pain in younger subjects. *Clin Rheumatol* 26: 75–80.