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# A 20 years of progress and future of quantitative magnetic resonance imaging (qMRI) of cartilage and articular tissues—personal perspective☆

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ABSTRACT

*Objective:* In 1994, the first article on quantitative magnetic resonance imaging (qMRI) of articular cartilage was published, and tremendous progress in image acquisition, image analysis, and applications has since been made. The objective of this personal perspective is to highlight milestones in the field of qMRI of cartilage and other articular tissues over these past 20 years.
*Methods:* Based on a Pubmed search of original articles, the authors selected 30 articles which they deemed to be among the first to provide an important technological step forward in qMRI of cartilage, provided a first application in a particular context, or provided mechanistic insight into articular cartilage physiology, pathology, or treatment.
*Results:* This personal perspective summarizes results from these 30 articles. Further, the authors provide examples of how qMRI of cartilage has translated to quantitative analysis approaches of other articular tissues, including bone, meniscus, and synovium/edema. Eventually, the report provides a summary of how the lessons learned might be applied to future clinical trials and clinical practice.
*Conclusions:* Over the past 20 years, quantitative imaging of articular tissues has emerged from a method to a dynamic field of research by its own. Continuing the qMRI biomarker qualification process will be crucial in convincing regulatory agencies to accept these as primary outcomes in phase 3 intervention trials. Once successful structural intervention will actually become available in OA, qMRI biomarkers may play an essential role in monitoring response to therapy in the clinic, and in stratifying disease phenotypes that respond differently to treatment.



## Main text

In 1994, the first article on quantitative magnetic resonance imaging (qMRI) of articular cartilage was published [1], and tremendous progress has since been made. This progress was related to technological refinement of image acquisition or image analysis, or to applications of qMRI to a specific scientific context in cartilage research. Several hundreds of imaging studies have since provided a great wealth of knowledge on articular tissue structure under both physiological and pathological conditions.

The objective of this review is to provide a historic perspective on the progress made, and to highlight milestones in the field of cartilage qMRI of articular cartilage and other articular tissues. Given previous comprehensive reviews on imaging in osteoarthritis (OA) and cartilage repair [2–8], the purpose of the present work was not to reiterate previous summaries, but to provide a personal

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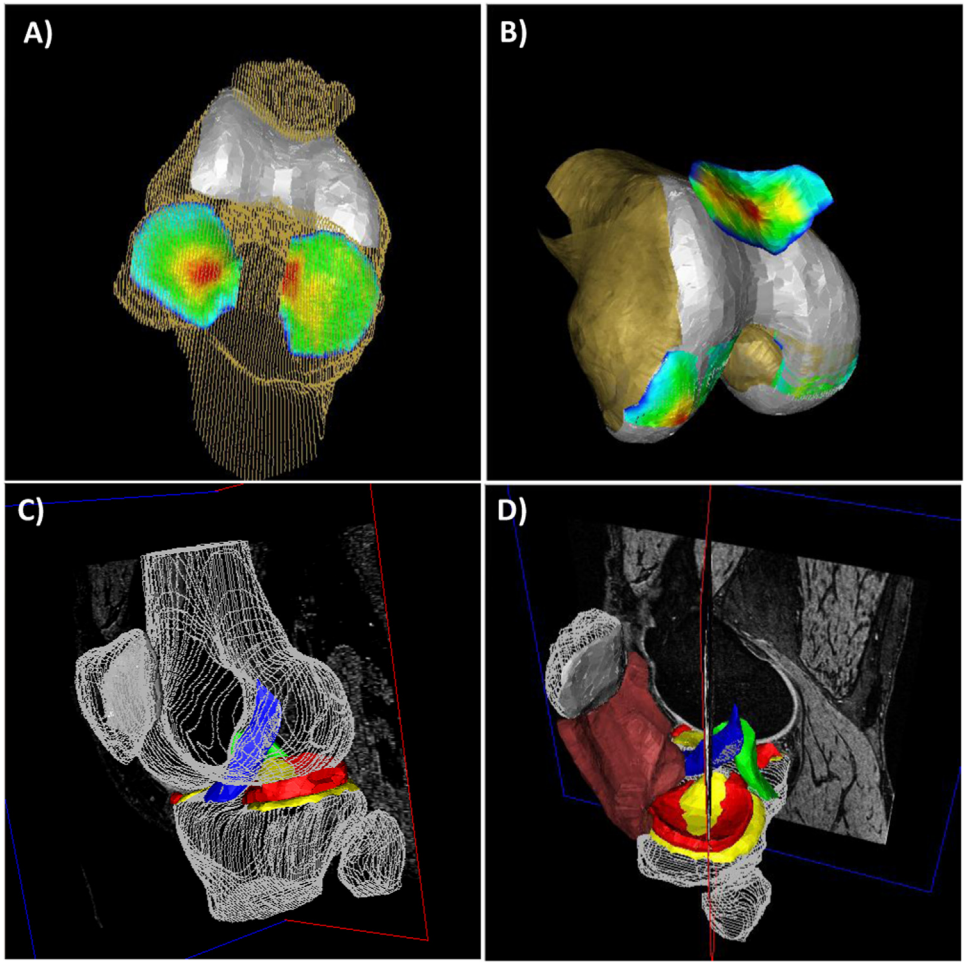


**Fig. 1.** 3D reconstruction of knees from MR imaging: (A) patellar bone (top), femoral bone, and tibial bone (bottom) shown as grids. The tibial articular surfaces are displayed as heat maps, with red indicating thick and blue thin cartilage cover. The femoral trochlea is reconstructed as a white surface. (B) Femoral bone shown in solid brown. The patellar articular surface is displayed as heat map, with color coding as in (A). The femoral trochlea and condyles are reconstructed as a white surface, with tibial articulating surfaces in color. (C) Patellar bone (left), femoral bone (top), and tibial bone (bottom) shown as grids. The tibial articular surface is diplayed yellow, the meniscus bright red, the anterior cruciate light blue, and posterior cruciate green. (D) Sample, color codes and structures as in (C), with original sagittal MR images shown in the blue frame, and the infrapatellar fat pad reconstructed in dark red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perspective on key articles, judged by the authors to be of particular relevance. No "objective," bibliometric measures were used to evaluate the importance of the work cited. Also, there was no intent to be "cartilage-centric" or to deny that OA is a disease that involves multiple articular tissues, as the purpose to provide a historic account with focus on key milestones in qMRI. For the purpose of this review, qMRI of articular cartilage will be defined as quantitative measurement of its geometric dimensions (i.e., cartilage volume and thickness; Fig. 1A and B) by MRI. Work on semi-quantitative grading of articular tissues (i.e., radiological scoring of lesions) [4,6,8], compositional analysis of cartilage (i.e., measurement of proteoglycan, collagen, or hydration [3,6,8]), or measurement methods and scoring systems focused on cartilage repair procedures [2] will not be considered, as each of these topics deserve a perspective on its own. In preparing the perspective, the authors searched the literature from Pubmed between 1994 and July 2015, using a variety of search terms; published conference abstract were not considered. A subjective choice of 30 cartilage qMRI publications was made (Table), based on whether the authors felt they were among the first to provide an important technological step forward with impact on future work, provided a first application in a particular context, and/or provided mechanistic insight into articular cartilage physiology, pathology, or treatment.

The main part of this historic perspective is structured in 4 sections (Table):

(1) Technological advances in qMRI of articular cartilage.
(2) Contributions to understanding cartilage physiology.
(3) Contributions to understanding cartilage pathology.
(4) Application in interventional trials.

In section (5), examples are provided of how this work has translated to qMRI approaches of other articular tissues, including (subchondral) bone, meniscus, and synovium/edema (Fig. 1C and D). In section (6), we summarize how the lessons learned might be applied to future clinical trials and clinical practice.

An "image" *(from Latin: imago) is an artifact that depicts or records visual perception, for example a two-dimensional picture, that has a similar appearance to some subject—usually a physical object or a person, thus providing a depiction of it (cited from Wikipedia)*. The perception of an image occurs at the interface between the outside world and the human brain, and hence is an interpretation of what is really there. The terms "image" and "imagination" are closely related, and the verb "to visualize" can mean "to image" or "to imagine." Yet, for "images" to be used in science or medicine, consensus needs to be established amongst "observers" on how the image information is to be interpreted.

**Table**
Authors' selection of 30 milestone articles in quantitative cartilage imaging, sorted historically within each of 3 categories

| | |
|---|---|
| *Technological advances in qMRI of articular cartilage* | |
| (1) Peterfy et al. [1] | First study to validate and assess the reliability of quantification of articular cartilage *volume* in cadaver knees, using fat-suppressed T1-weighted spoiled gradient echo (SPGR) imaging. |
| (2) Peterfy et al. [9] | First study to validate and assess the reliability of quantification of articular cartilage *volume* in a small joints (e.g., the metacarpophalangeal, MCP, and joint) using a small partial volume coil. |
| (3) Eckstein et al. [10] | First study to validate measurement of cartilage *thickness* in cadaver knees, accounting for out-of-plane deviations of thickness measurements in curved joint surfaces. |
| (4) Cohen et al. [11] | First study to provide a full 3D surface reconstruction of cadaver knee cartilage surfaces and to validate surface topography vs. stereophotogrammetry (SPG), a method with very high (μm) spatial accuracy. |
| (5) Burgkart et al. [12] | First study to validate and assess the reliability of quantification of articular cartilage *volume* in the knee in patients with severe knee osteoarthritis under in vivo conditions, prior to knee replacement. |
| (6) Eckstein et al. [16] | Proposal on a nomenclature for cartilage morphometry metrics by an international group of experts. |
| (7) Pelletier et al. [13] | First study to propose a subregional approach in measuring knee cartilage volume. |
| (8) Buck et al. [15] | First study to show that a location-independent method of measuring cartilage change (based on subregions) is more sensitive in detecting risk factors of OA progression than region-specific measures. |
| (9) Eckstein et al. [14] | First study to report sensitivity to change of knee cartilage subregions in a large core sample of Osteoarthritis Initiative (OAI) participants, and first to review quantitative cartilage imaging in the OAI. |
| (10) Schneider et al. [17] | Comprehensive validation and reliability study of the OAI water excitation double echo steady state (DESS) MRI sequence, by 4 segmentation teams using OAI pilot test–retest acquisitions. |
| *Contributions to understanding cartilage physiology* | |
| (11) Herberhold et al. [18] | First study to describe the in situ the time-dependent deformation of femoropatella cartilage in a human cadaver specimens with fully intact joint capsule (over 4 h of static deformation). |
| (12) Eckstein et al. [19] | First study to describe (patellar) cartilage deformation and recovery in vivo, shortly after physiological loading, and during/after multiple sets of in vivo loading. |
| (13) Waterton et al. [20] | First study to examine diurnal changes in knee cartilage thickness. |
| (14) Jones et al. [21] | First study to report cartilage volumes in healthy children, aged 9–18 years of age. |
| (15) Mühlbauer et al. [22] | First study to examine functional adaptation of knee joint cartilage (thickness) to mechanical stimuli, by comparing cartilage thickness in professional triathletes vs. physically inactive volunteers. |
| *Contributions to understanding cartilage pathology* | |
| (16) Wluka et al. [23] | First study to report knee cartilage volume loss in patients with symptomatic osteoarthritis. |
| (17) Cicuttini et al. [24] | First study to report cartilage loss to be an independent predictor of future knee replacement, providing the first evidence that a structural MRI outcome may be related to a clinical outcome. |
| (18) Raynauld et al. [25] | First study to directly compare the sensitivity to change and the correlation between quantitative cartilage imaging with radiography, the method thus far considered state of the art in clinical trials. |
| (19) Bruyere et al. [27] | First study to prospectively explore the relationship between quantitative cartilage loss in MRI and molecular markers of bone, cartilage, and synovial turnover |
| (20) Eckstein et al. [28] | First longitudinal multicenter observational study performed using 3 T MRI, relating 16 molecular markers and various structural measures to subsequent location-independent measures of cartilage loss. |
| (21) Sharma et al. [30] | First longitudinal study to report quantitative cartilage imaging markers to be more sensitive to revealing relationships with relevant risk factors (e.g., frontal plane malalignment and meniscus lesions) of disease progression compared with progression of semi-quantitative scores of cartilage damage. |
| (22) Hunter et al. [31] | First study reporting the 1-year natural disease progression rates in the first release of a subsample of OAI progression cohort participants with frequent symptoms and radiographic signs of knee OA. |
| (23) Reichenbach et al. [29] | First cross sectional study of a large population-based sample (the Framingham cohort) to report semi-quantitative scores of cartilage lesions to be more sensitive to the detection of early cartilage disease than quantitative measures of (subregional) cartilage thickness. |
| (24) Stannus et al. [26] | First study to report an association of serum levels of leptin with knee cartilage loss, indicating that leptin may represent an important link between obesity and cartilage health. |
| (25) Eckstein et al. [32] | First study to explore the longitudinal (4 years) trajectory of cartilage loss prior to knee replacement, using a nested case–control study design with adjustment for radiographic disease severity. |
| *Application in interventional trials* | |
| (26) Wluka et al. [33] | First double blind, randomized controlled trial (RCT) using quantitative imaging of cartilage as a structural endpoint, testing effectiveness of a nutraceutical (supplementary vitamin E). |
| (27) Raynauld et al. [34] | First double blind RCT to study structural effects of a potential disease modifying OA drug (DMOAD) on cartilage loss, measured quantitatively with MRI. |
| (28) Bennell et al. [35] | First double blind RCT to examine the effect of non-pharmacological secondary prevention (wedged insoles) on disease progression, measured quantitatively with MRI. |
| (29) Intema et al. [36] | First study to demonstrate a significant structural anabolic treatment response of articular cartilage (to mechanical joint distraction applied for 2 months), measured quantitatively with MRI. |
| (30) Eckstein et al. [37] | First study to demonstrate that location-independent analysis of cartilage thinning and thickening scores is more informative and sensitive in detecting treatment effects than (region-based analysis approaches, and to show that cartilage loss can be effectively reduced by intra-articular drug treatment. |

Please note that the sequence of articles mentioned in the text does not strictly follow the historic order used in the Table, but is in some part presented along themes.

This may be achieved by rule-based approaches to interpreting complex visual patterns, or by assigning grades of structural pathology to image representation, based on verbal descriptions or on pictorial atlases. When imaging is applied longitudinally to assess "change" in certain tissues, quantitative image analysis may demonstrate small increments of change on a continuous scale that may not be detected by the naked eye. This is of particular relevance in 3D imaging, where anatomical structures extend over several slices and the integration of through-plane information by the naked eye is challenging.

Before emergence of cartilage qMRI in 1994, little was known on the morphology and functionality of the tissue in vivo, and on its alterations in joint disease. Prior knowledge was based on ex-situ mechanical testing of cartilage specimens, animal experimentation, and indirect visualization by radiography, none of which are able to provide the depth of knowledge provided by direct

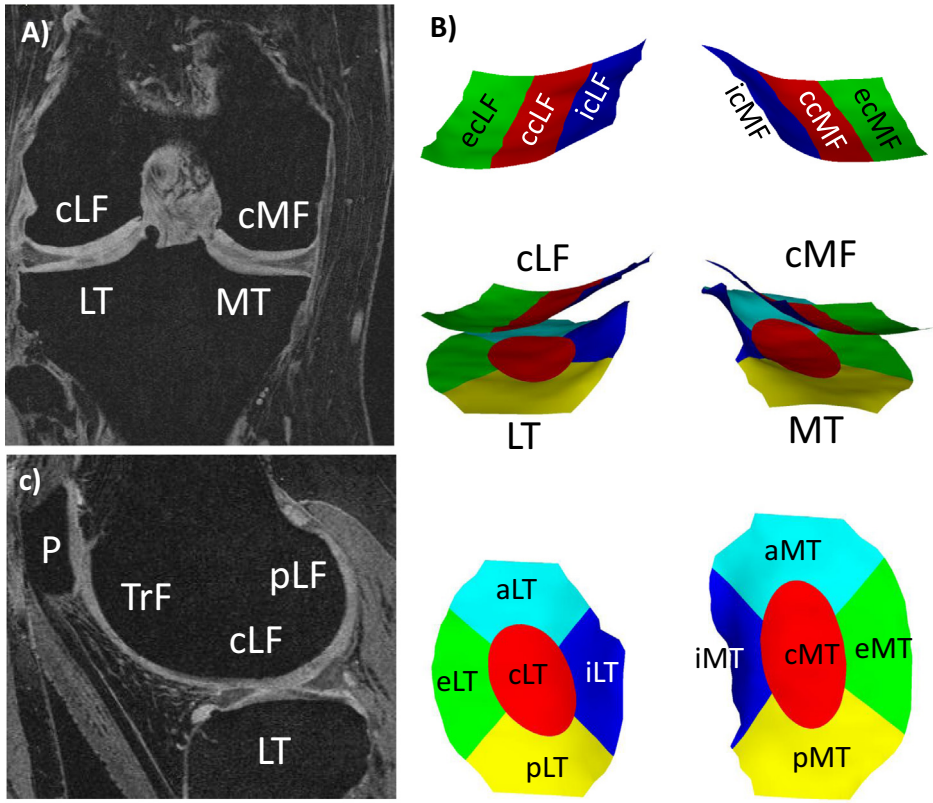


**Fig. 2.** Validated MRI sequences for quantitative analysis of articular cartilage and typical femorotibial subregions. (A) Coronal SPGR (or FLASH) sequence with water excitation, showing the medial tibial (MT), lateral tibial (LT), medial (central) weight-bearing emoral (cMF), and lateral (central) weightbearing femoral cartilage (cLF). (B) Specific implementation of femorotibial subregions: e, external; c, central; i, internal; a, anterior; p, posterior. (C) Sagittal DESS with water excitation showing the lateral tibial (LT), lateral (central) weight-bearing femoral (cLF) lateral posterior femoral (pLF), trochlear femoral (TrF), and patellar (P) cartilage.

delineation of the tissue in the living. The field therefore was underdeveloped compared to that of other musculoskeletal tissues, such as bone, for which Julius Wolff formulated a law of transformation as early as 1892. Also, relative to osteoporosis, monitoring disease status, and drug development were much less advanced in OA, not only lacking quantitative imaging methodology but also a discrete and undisputed clinical endpoint, such as bone fracture. Even today, no disease- or structure-modifying OA drug (DMOAD) has been approved by regulatory agencies, but some proof-of-concept studies currently underway raise hope that this may be achieved within the next 5–10 years. The current perspective focuses on current developments, but also aims to highlight scientific studies that have elucidated mechanisms of healthy cartilage development, physiology, and function "in vivo."

## (1) Technological advances in qMRI of articular cartilage

In 1994, Peterfy et al. [1] published the first validation and test of reliability (reproducibility) of cartilage volume quantification in the knee. The authors applied 3D MR imaging sequences at 1.5 Tesla (T) to knee specimens and then determined cartilage volumes from 3D reconstructions, using computer-aided segmentation and voxel summation. Accuracy was confirmed by comparison with direct quantification of cartilage volume from water displacement of surgically retrieved tissue (Archimedes principle). A year later, the authors validated volumetric cartilage measurements in a much smaller joint (metacarpophalangeal) using a small partial volume coil; again they reported small accuracy errors and good reliability [9]. Both studies used fat-suppressed T1-weighted spoiled gradient echo imaging (SPGR, fast low angle shot (FLASH), or T1-weighted fast field echo (FFE), and name depending on vendor) and this particular MRI sequence has since remained the mainstay of cartilage qMRI, and is since available on most clinical scanners (Fig. 2A).

In 1996, a 3D technique was presented that accounted for out-of-plane deviation of cartilage thickness measurements in curved knee joint surfaces [10]. Topographical cartilage thickness maps were provided for knee joint specimens and healthy volunteers using images with high in-plane resolution (0.31 mm), and thickness maps were compared with those derived from anatomical sections. The intra- and inter-observer reproducibility were found to be satisfactory both in the specimens and in healthy volunteers, and $<20\%$ of the tested image points found to deviate by $>0.5$ mm cartilage thickness in relation to the validation standard. Cohen et al. [11] performed full 3D surface reconstruction of the knee surfaces and reported average accuracies of 0.14 mm for subchondral bone surfaces, 0.22 mm for cartilage surfaces, and 0.31 mm for cartilage thickness in comparison with stereophotogrammetry (SPG), a method known to provide $<0.01$ mm spatial accuracy. The authors concluded that clinical MRI provides accurate measurement of cartilage thickness, contact areas, and surface curvature, and may hence be used to design computer models of load transmission and patient-specific biomechanical simulations on the effect of surgery.

Burgkart et al. [12] examined the accuracy of cartilage qMRI for the first time in patients with severe knee OA in vivo, prior to knee replacement. Fat-suppression of was achieved by water excitation rather than by a pre-pulse, shortening acquisition time (Fig. 2A). After knee replacement, tibial and patellar cartilage was resected, and the qMRI data compared with water displacement of the surgically retrieved tissue. A high linear relationship between both measurements was reported, with only a small systematic off-set,

and the estimated tissue loss was $>1000\,mm^3$ compared with data obtained in young, healthy volunteers.

It was later recognized that cartilage loss in OA is not uniform across knee cartilages, and therefore subregional approaches for measuring cartilage volume [13] in defined areas were developed. OA-related sensitivity to change of cartilage thickness in subregions (Fig. 2B) was reported in a large sample of Osteoarthritis Initiative (OAI) participants [14]; the same article also was the first to review cartilage qMRI technology applied to the OAI, a public data base providing longitudinal MRIs over up to 8 years in almost 5000 participants [14].

It was further recognized that the subregional pattern of cartilage loss varies between subjects, depending on the specific underlying pathology; therefore, a location-independent method of measuring cartilage thickness change was proposed. This methodology was termed "ordered values" (OVs) and is based on subregional analysis (Fig. 2B); it targets the greatest magnitude of subregional cartilage loss or gain in whichever region it occurred in a given joint [15]. The approach was shown to provide greater sensitivity in detecting risk factors of OA progression (e.g., malalignment, radiographic joint space narrowing (JSN)) than region-specific approaches did [15]. Further, the OV methodology is capable of separately describing regional cartilage thinning and thickening, potentially going on at the same time due to local cartilage swelling in early OA.

In 2004, an international group of experts proposed a nomenclature for regions of interest in the knee (Fig. 2) and for various cartilage morphometry metrics [16]. The intent was to facilitate communication within the scientific community and to provide recommendations as to which minimal methodological information should be provided in publications reporting qMRI metrics of articular cartilage. In another collaborative effort, in which 4 independent segmentation teams participated in a test–retest exercise on OAI pilot study data [17], double echo steady state (DESS) MRI imaging (Fig. 2C) was shown to provide cartilage volume and thickness measurement equivalent to previously validated [1,10–12] SPGR. Further, the DESS (Fig. 2C) showed reliability similar to SPGR (Fig. 2A), with the measurement variability between different MRI protocols and different image orientations being smaller than that between the segmentation teams [17]. Both DESS and SPGR (Fig. 2) are now commonly used in qMRI studies of articular cartilage [14].

**(2) Contributions to understanding cartilage physiology**

Although cartilage mechanical properties were thoroughly studied in vitro, only vague information on cartilage deformation in intact joints was available prior to the advent of qMRI. Herberhold et al. [18] were the first to study the time-dependent deformation of femoropatellar cartilage "in-situ," with a fully intact joint capsule (Fig. 3). Static loading was applied to a knee specimen continuously over 4 h with 150% body weight using a non-metallic compression apparatus (Fig. 3A). Cartilage thickness decreased exponentially and reached equilibrium in the central slice after approximately 3.5 h (Fig. 3B and C), with a total patellar cartilage volume reduction of almost 30%. Interestingly, only a small fraction of the final (3.5 h) deformation was reached during the first few minutes of loading, suggesting that little deformation occurs physiologically during short term loading [18]. Imaging was continued after removal of the load in 1 specimen, and the patellar cartilage displayed almost full recovery (98%) after 4 h.

To evaluate cartilage deformation in vivo, patellar cartilage volume was quantified after 1 h physical rest and then 3–7 min after a set of deep knee bends [19]. A 5% deformation of patellar cartilage was observed; with the time required for recovery during non-weight-bearing being approximately 90 min. Repeated sets of knee bends at intervals of 15 min maintained the same level of deformation, but they did not lead to further cartilage deformation [19]. Waterton et al. [20] found statistically significant diurnal changes in cartilage thickness maps when studying volunteers in the morning and evening. Thinning was, observed in the femorotibial and femoropatellar contact zones, and reciprocal cartilage thickening in the non-contact zones; the overall cartilage volume, however, remained unchanged during the day. The authors hypothesized this to result from negative intra-articular pressure, but it was alternatively suggested that interstitial fluid was displaced from load-bearing to non-load-bearing areas during standing.

Jones et al. [21] were the first to explore development and maturation of human cartilage, studying healthy children aged 9–18 years. They reported greater lateral than medial femorotibial cartilage thickness, and thicker cartilages in boys than girls at all ages. Self-assessed scores of physical activity were associated with greater knee cartilage volume. To assess the capacity of articular cartilage to functionally adapt to mechanical loading, Mühlbauer

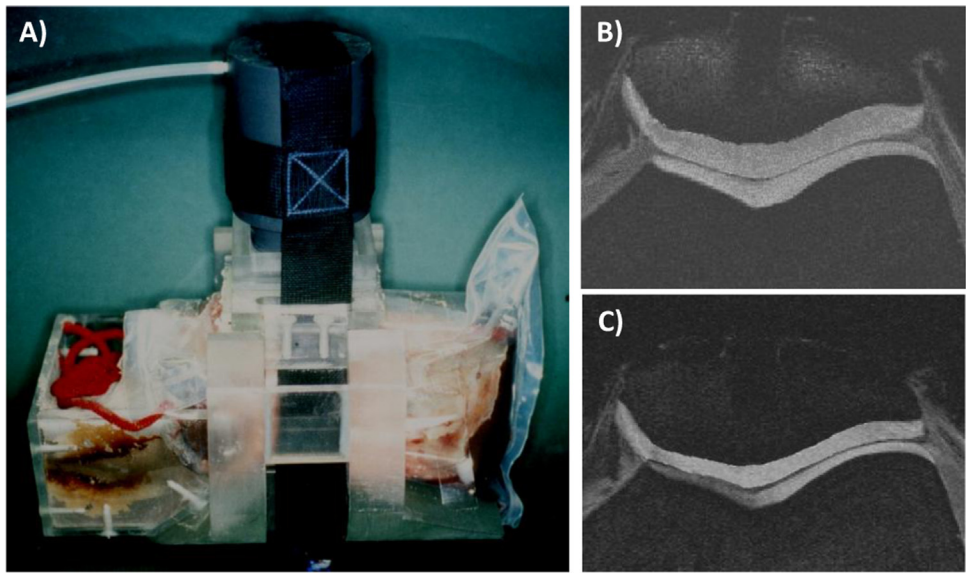


**Fig. 3.** Analysis of partellar cartilage compression in an intact joint under 4 h static loading. (A) Non-metallic compression apparatus holding a femoropatellar joint specimen. (B) Axial MRI acquisition (FLASH) before compression. (C) Axial MRI acquisition (FLASH) after 3.5 h of static compression with 1.5 × body weight.

et al. [22] studied professional triathletes and physically inactive volunteers ( < 1 h of physical activity per week throughout life). They did not find statistically significant differences in cartilage thickness between both groups, despite the substantial difference in the "mechanical loading histories." These results were unexpected in view of functional adaptation observed in other musculoskeletal tissues, such as bone, muscle, and tendon.

### (3) Contributions to understanding cartilage pathology

Wluka et al. [23] were the first to publish longitudinal cartilage volume change in patients with symptomatic knee OA; over a course of 2 years, tibial cartilage was reported to decrease by 5.3 ± 5.2%, with similar rates medially and laterally [23]. The same groups reported 2 years longitudinal tibial cartilage loss to be an independent predictor of future knee replacement [24], with subjects in the highest tertile of tibial cartilage loss having a 7.1 higher odds of surgery than those in the lowest tertile [24]. These results provided the first evidence that a structural MRI outcome may be related to a "hard" clinical outcome; the authors concluded that treatment targeted at reducing cartilage loss in symptomatic knee OA may delay knee replacement surgery.

In the first article to directly compare the sensitivity to change of quantitative cartilage imaging with the method thus far considered state of the art, with radiography [25], there was no statistically significant correlation between the change in medial compartment cartilage volume and that in medial radiographic JSW (standardized semiflexed x-ray). However, a later study by the same group [13] reported a strong correlation between central femorotibial cartilage volume change and medial JSW change [13]. The earlier study [25] reported rates of medial cartilage volume loss to be associated with a low baseline range of knee motion, high levels of knee pain and stiffness, and obesity [i.e., a higher body mass index (BMI)]. The second study [13] reported greater medial than lateral (central) femorotibial cartilage loss, and significant associations with female sex, baseline radiographic JSW, meniscal pathology, signal alterations of subchondral bone, and a high BMI. In an attempt to elucidate how obesity may contribute to knee OA, Stannus et al. [26] reported serum levels of leptin to be negatively correlated with knee cartilage thickness from q MRI. The BMI, trunk, and total body fat were also inversely associated with knee cartilage thickness, but these associations disappeared after adjustment for serum leptin, indicating that leptin may represent an intermediate in the association between obesity and cartilage health. Prospectively, leptin levels were associated with longitudinal thinning of medial tibial cartilage; the authors proposed that leptin acts in biphasic manner, inducing beneficial effects on cartilage physiologically, but causing tissue degradation when present in excess.

The first prospective study to explore the relationship between quantitative cartilage loss in MRI and molecular markers of bone, cartilage, and synovial turnover found an increase in CTX-II over 3 months to be significantly correlated with a 1-year decrease in medial tibial cartilage thickness [27]. However, a first multicenter study performed using 3 T MRI reported no significant relationship between any of 16 state-of-the-art molecular markers, compositional measures of cartilage, or meniscus measures with cartilage loss over 2 years [28]. This was despite the fact that this study [28] the first to use a location-independent classification system of "structural progression," and to separately assessed cartilage thinning and thickening using the location-independent ordered value (OV) method described above [15]. The strongest predictors of progression were low baseline cartilage thickness and radiographic JSN as well as varus malalignment [28].

In terms of methodological comparisons with semi-quantitative scoring of MRI structural pathology, 2 articles highlighted the specific strengths and limitations of each approach: a cross sectional study of a large population-based sample (the Framingham cohort) found only small difference in total or subregional femorotibial cartilage thickness between knees with mild radiographic OA [Kellgren Lawrence grade (KLG) = 2] vs. those without radiographic OA (KLG = 0), but there were statistically significant differences in semi-quantitatively graded focal cartilage lesions scores [29]. A longitudinal study, in contrast, reported qMRI of cartilage to be more sensitive over time in revealing relationships with risk factors of disease progression (e.g., malalignment and meniscus pathology) compared with the progression of semi-quantitative cartilage lesion scores [30]. Hence, qMRI outcomes appear to be inferior to semi-quantitative scores in characterizing cartilage disease status diagnostically, but appear to be more sensitive in longitudinal studies, likely due to greater precision of continuous measures.

Quantitative cartilage imaging has become one of the main structural outcomes in the OAI (NCT00080171) public data base [14]. The test–retest reliability of the OAI MR imaging protocol in the hands of various analysis groups has been mentioned previously [17]; the first article reporting 1-year natural disease progression in a subsample of the OAI progression cohort (participants with frequent symptoms and radiographic OA) reported standardized response means (SRMs) of ≤0.4 [31], with greater rates of cartilage loss in the medial femur than in the medial tibia, and greater loss in the lateral tibia than the lateral femur. As previously mentioned, qMRI data on 1- and 2-years rates of change of femorotibial cartilage plates and subregions (Fig. 2B) were reported in a larger core sample of the OAI progression cohort, and the greatest sensitivity to, change (standardize response mean: 0.51) for the 2 years observation period was observed in combined central medial tibial and medial femoral subregions (Fig. 2B). The measurements for these 600 progression cohort participants are publically available to the scientific community and can be downloaded from the OAI webpage [14]. Close to 200 knees in the OAI received surgical replacement between baseline and the 60 months follow-up time point) [32]: a nested case–control study examined the 4-year trajectory of femorotibial cartilage loss by qMRI prior to knee surgery, with adjustment for radiographic disease severity between cases and non-replaced control knees [32]. The study reported significantly greater cartilage loss in the medial femorotibial compartment of surgically replaced knees than in controls, particularly in the central medial tibia (Fig. 2B). This observation was made over 2 years prior to knee replacement, but did not extend to prior observation intervals [32]. The study confirmed that qMRI cartilage loss is important with respect to a socio-economically important clinical outcome [32]. The study also revealed greater rates of cartilage thickening prior to knee replacement compared with non-replaced controls by aggregating the negative and positive ordered values (OVs) in each subject to compose a location independent (total joint) thinning and thickening score [32]. These results highlight the value of a long follow-up in the OAI that now extends up to 92 months after baseline. Specific "cases" may be identified at later time points, with imaging outcomes being available for several years prior to the "event" of interest.

### (4) Application to interventional trials

Given the progress reported in previous paragraphs, cartilage qMRI has been probed to test the efficacy of therapeutic intervention. In a first double blind, randomized controlled trial (RCT) using qMRI as a structural endpoint, Wluka et al. [33] found that

2 years application of a nutraceutical (supplementary vitamin E) did not affect cartilage volume loss in relation to placebo-treated participants, and that dietary levels of antioxidants also had no effect on cartilage volume change [33]. The first double blind RCT to study structural effects of a potential DMOAD examined twice daily application of licofelone (200 mg) in comparison with naproxen, as control intervention [34]. No significant effect was observed on the primary structural outcome (i.e., medial cartilage volume loss), but loss in the lateral femorotibial cartilage was significantly reduced by licofelone. Licofelone-treated patients also displayed less reduction in radiographic JSW than those treated with naproxen, but the difference did not reach statistical significance. The authors therefore concluded that qMRI of cartilage was superior over radiography in showing DMOAD efficacy [34]. The first double blind RCT (NCT00415259) to analyze the effect of a non-pharmacological secondary prevention on qMRI disease progression (i.e., medial femorotibial cartilage volume loss) did not identify structural benefits for wearing laterally wedged insoles compared with flat control insoles [35]. In the same year, however, a first treatment study was published that demonstrated that an increase in cartilage thickness could be achieved by a "mechanical" intervention, in the compartment affected by radiographic OA [36]. This "anabolic" response was achieved by 2-month joint distraction with an external fixation frame in patients with late stage disease (mostly KLG = 3 and 4) aged $<60$ ($48 \pm 7$) years. qMRI revealed an 25% increase in cartilage thickness and a significant reduction in denuded bone areas 1 year later, accompanied by an increase in weight-bearing radiographic JSW [36]. This study thus provides an important "proof-of-concept" that reversal of cartilage loss is attainable. The patients treated by distraction also generally improved clinically, with the WOMAC increasing from 45 to 77 points, and the VAS decreasing from 73 to 31 mm over 1 year [36]. Finally, a recent double blind, placebo-controlled RCT (NCT01033994) tested the efficacy and safety of intra-articular sprifermin as a DMOAD, using cartilage qMRI as structural endpoint [37]. In that study, the primary location-specific outcome (cartilage loss in combined central medial tibial and femoral subregions; Fig. 2B); failed to demonstrate a significant treatment effect of sprifermin vs. placebo injections over up to 12 months of observation whereas in line with a previous RCT [34], a significant DMOAD effect was noted in the lateral femorotbial compartment. However, subject-specific, location-independent analysis of ordered values [15] and subregional cartilage thinning and thickening scores [32] was more sensitive and informative in studying the treatment effect than the primary analysis approach. Analysis of the thinning score showed that cartilage loss was effectively reduced in patients treated with sprifermin, and analysis of the thickening score demonstrated that cartilage thickness increased more strongly in patients treated with sprifermin compared with placebo-treated patients [37].

## Quantitative MR imaging of other articular tissues

qMRI approaches have not only been applied to cartilage, but also to other articular tissues (Fig. 1C and D); the following paragraph thus provides some key examples of qMRI technology being translated to the "whole joint" and how this may contribute to a more comprehensive understanding of structural pathology in OA.

### *Bone*

Structural measures of trabecular bone were shown to display significant variation in patients with varying degrees of knee OA, with different patterns of structural alterations in the distal femur and proximal tibia [38]. Over a 2-year longitudinal observation period, a relationship was demonstrated between trabecular bone changes and those in cartilage volume [39]. Further, the bone–cartilage interface has drawn considerable interest in context of OA pathophysiology. Subchondral bone area expansion has been suspected to be a primary driver in the disease process, and to be associated with the severity of knee OA and risk factors such as age, BMI, or malalignment [40]. Recent work demonstrated that complex measures of bone shape differentiated knees at risk of incident knee OA from knees of non-incident controls [41], and that change in bone area displayed greater sensitivity to OA progression than change in cartilage thickness or radiographic JSW did [42]. qMRI approaches of measuring bone marrow lesions (BML) volume found larger baseline BMLs to be associated with greater baseline knee pain, baseline JSN and JSN progression, and change in BML volume was positively associated with change in knee pain [43].

### *Meniscus*

A 2-dimensional qMRI technology revealed that meniscal position (extrusion) contributed to variability observed in radiographic JSN, and that change in meniscal position contributed to longitudinal reduction in radiographic joint space width [44]. The same measure of meniscal extrusion was reported to be positively associated with greater subsequent cartilage loss [45], and measurement of meniscus height revealed presence of meniscus "hypertrophy" in subjects with end-stage knee OA [46]. A 3-dimensional qMRI of the meniscus (Fig. 1C and D) found extrusion to be associated with knee pain [47] and radiographic knee OA status [48]. Such qMRI meniscus metrics were recently shown to be highly sensitive to 2-year longitudinal change in OA knees that displayed radiographic joint space narrowing (JSN) at baseline [49].

### *Synovium and adjacent articular structures*

Inflammation is today thought play a more important role in OA than previously believed [50] and is therefore growing interest in qMRI analysis of synovial thickening, as a measure of synovitis [51]. Synovial volume was reported to be related to the radiographic status of knee OA and to BML volume [52]. Since synovitis is often associated with knee joint effusion, effusion volume represents a measure of interest, and qMRI measurement of effusion volume was shown to be consistent with phantoms and joint fluid aspiration [53]. Being closely related to the synovial membrane, the infrapatellar fat pad (IPFP) has recently become a focus of interest (Fig. 1D) [54]. The IPFP is suspected to play an endocrine role in knee OA, by causing synovitis through a mechanism of intra-articular adipokine secretion. IPFP volume has been determined quantitatively (Fig. 1D), in healthy subjects and in patients with knee OA [55]. Its relationship with knee symptoms, however, is [56] controversial [57,58], and its precise role in the pathophysiology of knee OA is under intense current investigation [54].

## Future perspective

Over the past 20 years, quantitative imaging of articular tissues has emerged from a method to a dynamic field of research by its own. Technological refinement and the translation of measurement methodology to other articular tissues have greatly improved the understanding of cartilage and whole joint physiology and pathology. These last 2 decades have seen considerable progress in characterizing the determinants of cartilage

development and maturation, deformation and function, functional adaptation, structural progression in OA, its interplay with different tissues in disease progression, and the relationship of articular structures with clinical outcomes. Novel quantitative MRI-based imaging biomarkers such as cartilage volume and thickness have been developed to replace conventional measures of structural progression, such as reduction in radiographic joint space width, in clinical trials [5,7,8,59]. These new potential "surrogate" markers are currently undergoing further biomarker qualification in side-by-side tests with molecular markers from serum and urine [60], to study whether they display change concurrent with an/or are predictive of symptomatic and radiographic progression of knee OA. As a result of these efforts, there now is growing evidence that sensitive qMRI measures of structural progression can be effectively applied in multicenter studies, are related to important clinical outcomes, and are associated with symptomatic progression of OA. Such qMRI measures already play a key role in the internal decision making by pharmaceutical companies as to whether specific drugs are taken to the next phase of the drug development and approval process. Continuing the qMRI biomarker qualification process will be crucial in convincing regulatory agencies to accept these as primary outcomes in phase 3 intervention trials. Once DMOADs may actually become available, qMRI biomarkers will play an essential role in monitoring response to therapy in the clinic, and in stratifying disease phenotypes that respond differently to treatment. Eventually, qMRI approaches may enable more effective and personalized therapy to be applied to the patient.

## Contribution statement

Both authors made substantial contributions to:

(1) the conception and design of the debate and this summary article,
(2) drafting the article or revising it critically for important intellectual content, and
(3) final approval of the version to be submitted.

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