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Quantitative Radiologic Imaging Techniques for Articular Cartilage Composition: Toward Early Diagnosis and Development of Disease-Modifying Therapeutics for Osteoarthritis

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Introduction

Osteoarthritis (OA) is the most common degenerative joint disease affecting articular cartilage and other joint tissues, resulting in serious morbidity and large socioeconomic impact (1–3). In the US, 27 million people experienced OA in 2005 (4). The total cost attributed to arthritis and other rheumatic conditions in the US was 128 billion dollars in 2003 (5,6). Due to an aging population and increasing obesity rates, OA will become even more prevalent in the next decades with an estimated 67 million Americans expected to be diagnosed with arthritis by 2030 (7). The final treatment option for OA is joint replacement, which is associated with complications, limited durability, and contributes to the high costs of OA.

Consequently, current OA research focuses on strategies that may be disease modifying, such as disease-modifying osteoarthritis drugs, chondrocyte implantation, stem cell therapy, or high tibial osteotomy (8–10). Attention is also focused on measures that may prevent or delay OA onset, including lifestyle interventions. These strategies all target OA at an early stage when they are most effective, thereby avoiding or delaying joint replacement.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Gold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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In order for therapeutic approaches to OA to be successful, monitoring of their effectiveness with accurate, sensitive, and objective imaging techniques is essential. Clinical OA measurements, such as pain, remain important, but are subjective and correlate poorly with disease severity (11,12). Radiography is used to stage and follow OA, but it cannot depict articular cartilage directly and correlates weakly with cartilage damage on arthroscopy (13,14). Furthermore, radiography is incapable of detecting early OA and subtle OA changes (15,16), and often does not correlate with OA symptoms (17,18).

Magnetic resonance imaging (MRI) is useful in OA because cartilage and other joint structures can be assessed for morphologic changes more reliably than on radiography (19,20). Several semiquantitative MRI scoring systems for OA have been developed, such as the Knee Osteoarthritis Scoring System (21), the Whole-Organ Magnetic Resonance Imaging Score (22), the Boston Leeds Osteoarthritis Knee Score (23), and the MRI Osteoarthritis Knee Score (24,25). Cartilage segmentation followed by thickness or volume measurements increase sensitivity further (26,27). Morphologic changes, however, are not always present in early-stage OA and may not change significantly with disease progression. In addition, conflicting reports have been published on the association between cartilage defects on morphologic MRI and pain or other OA symptoms (28,29). Therefore, MRI methods that rely on morphology may fail to capture early OA onset or subtle changes in disease severity (30). Because of the limitations of radiography and traditional MRI methods, there is need for new imaging modalities to not only advance our understanding of the pathogenesis of OA, but to provide novel end points to accelerate development of therapies. In the future, use of imaging to identify asymptomatic individuals in a “pre-OA” state may identify individuals for whom therapeutic intervention could prevent the subsequent development of OA.

Novel imaging techniques that enable measurement of the biochemical composition of cartilage rather than its morphology show promise to fulfill this need (31,32). These techniques offer numerical outcome measures that can be used as imaging biomarkers for cartilage quality in research on OA and other joint diseases. In addition, they may enhance understanding of the pathogenesis of OA. A recent report suggests that quantitative MRI may correlate better with knee pain in early OA (33). The majority of quantitative imaging techniques for cartilage composition are MRI-based, but recently computed tomography (CT) arthrography was also shown to be a suitable imaging modality for this purpose (34). In addition, quantitative imaging techniques are also applied to other tissues, such as menisci (35–37) and intervertebral discs (38,39). Most research, however, has been performed on articular cartilage of human knee joints.

This article presents the principles of quantitative imaging techniques for cartilage composition of the human knee, followed by a description of the most commonly used techniques, their advantages and limitations, as well as reported applications.

Principles of quantitative cartilage imaging

Hyaline articular cartilage is largely acellular as chondrocytes constitute only 4% of its wet weight (40). The main components of hyaline cartilage are water (65–85%), the extracellular

matrix consisting of type II collagen (15–20%), and proteoglycans (PGs) (3–10%) (41,42) (Figure 1A). Hyaline cartilage can be subdivided in 3 layers: the superficial, middle, and deep layer. In healthy cartilage, PG density and the orientation of the collagen fibers vary by location within the cartilage layer and regionally within the joint (41,43–45) (Figure 1A).

PGs mainly consist of glycosaminoglycans (GAGs) that are negatively charged due to ionized sulfate and carboxyl groups. These strong negative electrostatic charges, collectively responsible for the so-called fixed-charge density, are important contributors to the structure and biomechanical properties of articular cartilage (40). They allow GAG molecules to be fixed to the extracellular matrix and attract positive ions that attract water molecules, resulting in a swelling pressure of cartilage. This tendency to expand is counteracted by the surrounding collagen mesh-work and this balance between swelling pressure and collagen tension contributes to the tremendous tensile and compressive strength of hyaline cartilage under normal physiologic conditions (40–42,46).

It has been shown that in the early stage of OA and other hyaline cartilage diseases, PGs and GAGs leak from the cartilage and the collagen fibers change in size and orientation, allowing more water and less restricted water diffusion into the cartilage. These initial disease processes occur without macroscopic alterations in cartilage morphology (31,32) (Figure 1B). When cartilage disease progresses, morphologic changes (thinning and defects) of the cartilage appear (Figure 1C). Recently, MRI techniques have been introduced that are capable of measuring changes in cartilage composition before morphologic changes occur. These techniques all provide quantitative measures that correlate with collagen and PG content. Some techniques are believed to specifically correlate with the GAG component of PG, whereas other techniques correlate with water content and with collagen content and orientation. Several MRI methods have been proposed, each providing different outcome measures that can be used as imaging biomarkers.

The quantitative MRI techniques for cartilage composition require postprocessing algorithms to derive the outcome measure in the specific cartilage region of interest. Consequently, the underlying mathematic modeling may impact the quality and reliability of the biomarker. For example, it has been demonstrated that calculation of T1 relaxation times in quantitative cartilage MRI is improved by applying an automated registration algorithm (47,48).

In addition to the various MRI techniques, it has been shown that CT provides a quantitative outcome measure for cartilage biochemical status (34). Specific features and selected applications of quantitative MRI and CT techniques for cartilage composition are discussed below. Outcome measures, clinically relevant biochemical correlates, reported typical outcome values for healthy and OA-diseased cartilage, and advantages and disadvantages of each technique are summarized in Table 1.

Quantitative MRI techniques for cartilage composition

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)

The dGEMRIC mechanism makes use of the repulsive force between a negatively charged contrast agent (gadopentate dimeglumine) and negative charges on the GAGs, resulting in the contrast agent accumulating in cartilage inversely with GAG content (49). The outcome parameter is T1 relaxation time (usually averaged for the pixels in a region of interest: the dGEMRIC index). T1 relaxation time is reduced by the contrast agent and consequently is lower in areas with decreased GAG content compared to healthy cartilage (Figure 2A). The contrast agent is commonly administered intravenously using a double dose (0.2 mmole/kg [50]), after which the joint is exercised to promote contrast distribution into the synovium and joint cavity. For knees, a 90-minute delay between contrast injection and image acquisition is usually applied to achieve a semi-equilibrium state between contrast agent and cartilage (51). It has been reported that precontrast imaging is unnecessary (52,53). Variations on the dGEMRIC protocol have been reported, with the contrast injected intraarticularly (54,55), the contrast agent dose changed (50,56), and the length of delay optimized for other joints (56). Image acquisition is aimed at calculating the dGEMRIC index in the cartilage, and several MRI pulse sequences can be applied (57–59) with variable flip angles (60) or inversion times (57). Recently, time-efficient 3-dimensional (3-D) pulse sequences were applied that allowed coverage of the entire joint (57–59).

dGEMRIC has been validated largely with in vitro experiments, demonstrating a good correlation with GAG content. In vivo validation studies of dGEMRIC, however, are lacking, except for one study by Watanabe et al in which the difference between T1 relaxation time before and after contrast administration was found to correlate with GAG content of biopsied cartilage determined by liquid chromatography in 9 patients after autologous chondrocyte implantation (ACI) (61). When performed according to a standardized protocol, reproducibility of dGEMRIC was found to be good in several studies in healthy and OA subjects (62–64). It has been shown recently that dGEMRIC is associated with change in cartilage thickness over time (65).

dGEMRIC has been applied in studies on the influence of anterior cruciate ligament (ACL) tear (66,67), femoroacetabular impingement (68), and developmental dysplasia of the hip (69,70) on cartilage quality and OA pathogenesis. It was also used to study the OA disease-modifying potential of oral (71) and intraarticular medication (72), high tibial osteotomy (73), and weight reduction (74), and to followup cartilage repair with (matrix-associated) ACI in the knee (75) and ankle (76). In the field of rheumatoid arthritis, dGEMRIC has been used to visualize early cartilage damage in finger joints (77) and to assess the therapeutic effect of tumor necrosis factor inhibitors (78).

dGEMRIC is regarded as the best available imaging tool for indirect GAG measurement in vivo. There are, however, disadvantages of dGEMRIC mainly related to the contrast agent that increases costs and is potentially dangerous for patients with impaired renal function. Total examination time is extremely long due to the required delay between contrast administration and image acquisition (Table 1). Finally, rate and degree of contrast accumulation in cartilage may be influenced by factors other than cartilage GAG content,

such as collagen content and orientation (79,80), pharmacokinetics (81), and type and duration of the exercise (56,82).

T2 mapping

T2 mapping is regarded as the best method to measure collagen content (measured by signal intensity) and orientation (expressed by anisotropy) (83,84). In healthy cartilage the collagen network exhibits low signal intensity on T2-weighted MRI. In the earliest stages of cartilage disease, damage occurs to the cartilage matrix, causing loss of collagen content as well as a disorganization in its orientation, reflected in elevated T2 relaxation times (85) (Figure 2B).

Image acquisition in T2 mapping is usually performed using multiple spin-echo sequences at different echo times (83). Several recent alternatives have been proposed that yield full joint coverage within a relatively short acquisition time (86–89). In addition, double-echo steady-state was recently introduced as a time-efficient 3-D T2 mapping sequence with simultaneous acquisition of apparent diffusion coefficient values in cartilage that provide a measure of water diffusion (90,91).

In a recent multicenter multivendor study by Mosher et al, reproducibility of T2 mapping was found to be moderate to high in OA patients and normal controls (92). Previous validation studies of T2 mapping in vitro (84,93,94) and in vivo (85,95,96) have demonstrated that T2 mapping is a reliable method for quantification of early changes in collagen content and orientation. Although many authors have suggested T2 mapping to specifically correlate with collagen (83), some studies have also found a relationship with PG content (97–99).

T2 mapping has been used frequently as an outcome measure in clinical studies. Examples in the knee include T2 mapping to assess cartilage quality after ACL reconstruction (100), and cartilage repair procedures such as ACI (101) and microfracture (102,103). Abnormal T2 relaxation times have been reported to correlate with knee malalignment (104), meniscal pathology (105), and progression of knee OA (106). In the hip, T2 mapping was shown to be an indicator of early cartilage degeneration in patients with hip dysplasia (107) and slipped capital femoral epiphysis (108), whereas in the ankle it was mainly used to followup cartilage repair (109–111). T2 mapping is also incorporated as an imaging biomarker in large-scale epidemiologic studies on knee OA, such as the Osteoarthritis Initiative (33,112,113) and followup measurements of the Rotterdam Study (114,115).

T2 mapping shows high correlation with collagen content and orientation without the need for contrast administration (Table 1). Therefore, it provides information on cartilage quality that may be complementary to GAG-specific techniques. Drawbacks include magic angle effects (116) that may render T2 relaxation times inaccurate in certain areas of the joint (117). Another potential disadvantage is the fact that PG depletion has been suggested to occur earlier in the OA disease process than collagen loss by several reports (118–120). Therefore, T2 mapping may possibly detect cartilage changes later than GAG-specific techniques. It has been suggested that isolated PG depletion from cartilage may be reversible and more amenable to repair than cartilage with a structurally damaged collagen matrix (83).

T1rho mapping

T1rho mapping, also described as relaxation in the rotating frame, uses a constant radio frequency field referred to as a “spin lock” pulse to change relaxation rates of water associated with large macromolecules in cartilage. As T1rho relaxation time is sensitive to protons associated with PG and GAG, several authors have suggested a direct relationship between T1rho relaxation time and PG/GAG concentration (121). Decreased GAG content may lead to increased mobile proton density in bulk water and increased T1rho relaxation times (Figure 2C).

Reproducibility of T1rho mapping was found to be moderate for the femorotibial joint, but substantially better for patellar cartilage regardless of OA stage (92,122). The inverse relationship between T1rho relaxation time and PG/GAG content was found in several in vitro bovine cartilage experiments (123,124) and ex vivo human cartilage specimen validation studies (97,125), but the strength of the reported correlations varies (97,123,126,127). Several recent in vivo studies have also reported inconsistent correlation coefficients (range 0.2–0.61) for the relationship between T1rho relaxation times and GAG measurements (98,99,128). These differences between in vitro and ex vivo results compared to the in vivo results may be caused by the differences between preclinical and clinical T1rho sequences used for these studies (129).

Applied in clinical knee OA research, elevated T1rho relaxation times were found to correlate with age (130) and clinical OA scores (131), as well as predicted OA progression after 2 years followup (106). After ACL tears, T1rho relaxation times in femorotibial cartilage were found to be significantly increased generally (67) and in specific areas overlying bone marrow edema–like lesions (132), as well as in patients following ACL reconstruction (133). T1rho was also shown to be feasible for monitoring of cartilage repair procedures such as microfracture (102) and mosaicplasty (134). In several studies by Souza and colleagues, T1rho was sensitive to alterations in knee cartilage composition due to various loading conditions, such as jumping tasks (135), acute loading (136), and unloading (137). T1rho relaxation times were found to be decreased immediately following 30 minutes of treadmill running (138), and elevated 48 hours and 3 months after marathon running (139). Outside the knee, T1rho was able to detect biochemical differences in acetabular cartilage between normal and cam-type femoroacetabular impingement hips (140).

Although the exact biochemical correlate in terms of cartilage biochemical composition is still debated, T1rho has been advocated as a method to noninvasively measure cartilage GAG content without a contrast agent (Table 1). A disadvantage of T1rho is the large radio frequency power applied that may cause tissue heating at higher field strengths (122,141).

Ultrashort echo time (UTE)

Important musculoskeletal tissues such as cortical bone, tendons, ligaments, menisci, and the deepest layers of articular cartilage have short intrinsic T2/T2* relaxation times and produce little or no signal on most conventional T2-weighted sequences (142). UTE MRI applies 20–50-fold shorter TEs so that signals from short T2/T2* relaxation time tissues can be detected (143,144). This enables visualization of the deepest cartilage layers, including the calcified

zone (Figure 3). Furthermore, UTE offers the possibility to study the osteochondral junction and subchondral bone structure that both are believed to play a role in the pathogenesis of OA and cartilage damage (145). Novel UTE sequences also enable T1 and T1rho measurements in deep cartilage layers (146) or yield constant signal intensity data sets (147). Reproducibility of UTE T2* mapping of human articular cartilage in vivo was reported as good in a study of 11 asymptomatic subjects (148).

Although UTE is a promising method that offers assessment of the entire cartilage layer, the technology is still evolving and there have been no reports on its application as an outcome measure in clinical studies. Disadvantages include lengthened scan times and several other challenges related to MRI technique and physics that can reduce image quality (149) (Table 1).

GAG-specific chemical exchange saturation transfer (gagCEST)

Specific MRI sequences acquire independent signals from 2 water pools: free water and macromolecule-bound water. Interactions between these water pools result in a decrease of free water signal, the extent of which can be analyzed and used as a measure of macromolecule content in certain tissues. This MRI effect is called magnetization transfer (MT) (150). In cartilage, MT occurs between water bound to the collagen fibers and free water (151).

CEST is an adaptation of MT featuring selective magnetic saturation of exchangeable protons of specific molecules. Applied in cartilage, hydroxyl residues of GAG are excited to provide a direct measurement of GAG content (gagCEST) (151). The outcome measure in gagCEST is usually expressed as an asymmetry value or percentage, whereby lower percentages indicate less GAGs in the cartilage matrix.

The technique has been validated in vitro by comparing the results of gagCEST in healthy versus GAG-depleted cartilage and to sodium signal (151). In vivo, results of gagCEST have been compared to sodium MRI of healthy and diseased cartilage (152), and the difference between gagCEST outcomes at 3T and 7T have been assessed (153). In clinical research, gagCEST has been primarily used to investigate effects of knee cartilage repair strategies (152,154) (Figure 4). A recent cadaver study by Schmitt et al also suggested feasibility of gagCEST in the ankle (155).

GagCEST is a promising technique to quantitatively measure GAG depletion of cartilage in early cartilage disease. GagCEST is applicable on 7T and 3T MR systems (152–155), but drawbacks of gagCEST include its technical complexity and need of sophisticated postprocessing tools. Although gagCEST is feasible at 3T MR systems, acquisition is very difficult compared to 7T MR systems and might not be possible at all on 1.5T scanners due to different relaxation properties of water at different MR field strengths (152,153) (Table 1).

Sodium MRI

Unlike previously discussed MRI techniques that rely on proton (^{1}H) imaging, sodium MRI measures sodium (^{23}Na) signal (156). As positive sodium ions are associated with

negatively charged GAGs of the extra-cellular matrix (157), sodium MRI outcomes correlate with GAG content. GAG loss from cartilage in early cartilage degeneration is accompanied by reduced sodium concentration resulting in decreased sodium MRI signal (158) (Figure 2D).

Sodium imaging has been validated in vitro, demonstrating its sensitivity and specificity in detecting small differences in GAG concentration (157,159). It has been used both in vitro and in vivo to assess its potential to measure cartilage GAG content (49,160).

Despite good reproducibility in healthy volunteers and OA patients (161,162), sodium MRI is used infrequently as an outcome measure of cartilage GAG content in clinical research, due to several limitations, i.e., less favorable magnetic properties and a much lower concentration render sodium signal-to-noise ratio and in-plane resolution low unless the magnetic field strength is increased (158), special transmit and receive coils are used, and acquisition time is prolonged (163) (Table 1).

Nevertheless, several groups have applied sodium MRI in clinical studies to determine GAG content, mainly for cartilage repair assessment (152,154,164,165) (Figure 4C). Recently, fluid-suppressed sodium MRI at 7.0T was shown to distinguish healthy subjects from OA patients more accurately than conventional sodium MRI sequences (166).

Quantitative CT arthrography

Interest in quantitative CT arthrography to measure cartilage quality has recently increased (167,168). Like dGEMRIC, quantitative CT arthrography, also referred to as delayed quantitative CT arthrography, uses the inverse relation between a negatively charged contrast agent (ioxaglate) and GAG content in cartilage (34). The quantitative outcome of CT arthrography is the radiographic attenuation measured in Hounsfield units and is higher in GAG-depleted compared to healthy cartilage (Figure 5). In CT arthrography, the contrast agent is injected intraarticularly and is also used for cartilage delineation and segmentation (168,169). After contrast injection, the patient actively moves the joint to promote contrast distribution throughout the joint cavity. The reported delay between contrast administration and CT acquisition varies (34,169), but is shorter than dGEMRIC (51).

CT arthrography in humans has been validated in a recent ex vivo study in which radiographic attenuation on CT arthrography was correlated with GAG content in cartilage determined by a reference test (34). A recent in vivo study showed that CT arthrography correlates well with dGEMRIC T1 relaxation times in patients with knee symptoms (169). The reproducibility of CT arthrography has not been investigated yet, probably due to the relatively high amount of ionizing radiation used by most groups to obtain CT arthrography. It was demonstrated, however, that accurate measurement of overall cartilage quality is feasible with low-radiation dose CT arthrography protocols (170).

CT arthrography needs further optimization before it may serve as an outcome measure in clinical research. Despite ionizing radiation, the technique has some important advantages over MRI: short acquisition time, relatively wide availability, low costs, and high in-plane resolution. Its ability to simultaneously acquire high-resolution information on cartilage and

the underlying bone may be utilized to study the proposed role of subchondral bone in the pathogenesis of OA and cartilage damage (171) (Table 1).

Discussion and future perspectives

Quantitative MRI and CT techniques that measure cartilage composition in early disease stages are available. All techniques have a great potential to evolve further and be implemented increasingly in clinical research on OA. Even an application in patient care for specific clinical decision-making scenarios is foreseeable in the near future. Most techniques need thorough validation of in vivo measurements against in vitro reference standards, and studies comparing different techniques within the same subject are lacking. Future research should focus on larger-scale validation and comparison of these techniques. Quantitative imaging research needs to establish correlations with clinical symptoms and predictive value for clinical outcomes. These techniques will play a pivotal role in future research on and development of next-generation therapeutics for OA and other cartilage diseases. Ultimately, imaging could be used to guide clinical decision making by identifying individuals in a “pre-OA” disease state, for which intervention with a future disease-modifying therapy could prevent the development of OA.

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Significance & Innovations

- There is great need for imaging to advance our understanding of the pathogenesis of osteoarthritis (OA), to provide end points to accelerate development of therapeutics, and to ultimately guide clinical decision making.
- A variety of innovative magnetic resonance imaging (MRI) and computed tomography techniques to measure cartilage composition are available, correlating with cartilage matrix elements (collagen and proteoglycans/ glycosaminoglycans) that are affected in early disease stages.
- The role of quantitative imaging techniques in OA is emerging because they detect cartilage disease at earlier stages than radiography and conventional MRI, and provide outcome measures that can be used as imaging biomarkers in clinical research.
- Quantitative imaging techniques for cartilage composition are likely to play a pivotal role in future research and development of disease-modifying therapy for arthritis.

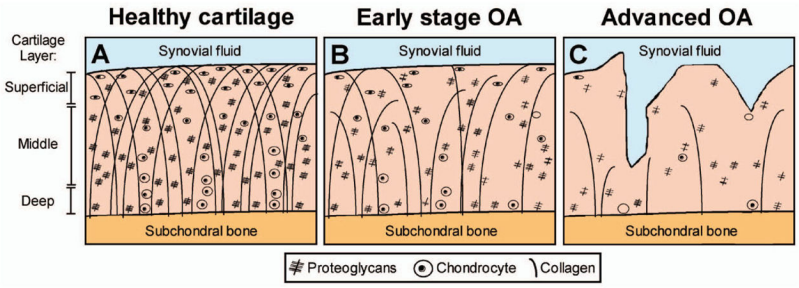

Figure 1.

Schematic representation of articular cartilage composition and morphology in healthy (**A**), early-stage osteoarthritic (**B**), and advanced-stage osteoarthritic cartilage (**C**). In healthy cartilage (**A**), the orientation and density of the collagen fibers varies by location within the cartilage layer and regionally within the joint. Relative to the articular surface, their prevailing orientation is parallel in the superficial layer, oblique in the transitional (middle) layer, and perpendicular in the deep radial zone. Similarly, the concentration of proteoglycans varies according to location and is highest in the middle layer. In early osteoarthritis (OA) (**B**), proteoglycans and glycosaminoglycans leak from the cartilage and the collagen fibers change in size and orientation. These initial disease processes occur without macroscopic alterations in cartilage morphology. When OA progresses (**C**), morphologic changes (thinning and defects) of the cartilage appear. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22316/abstract.

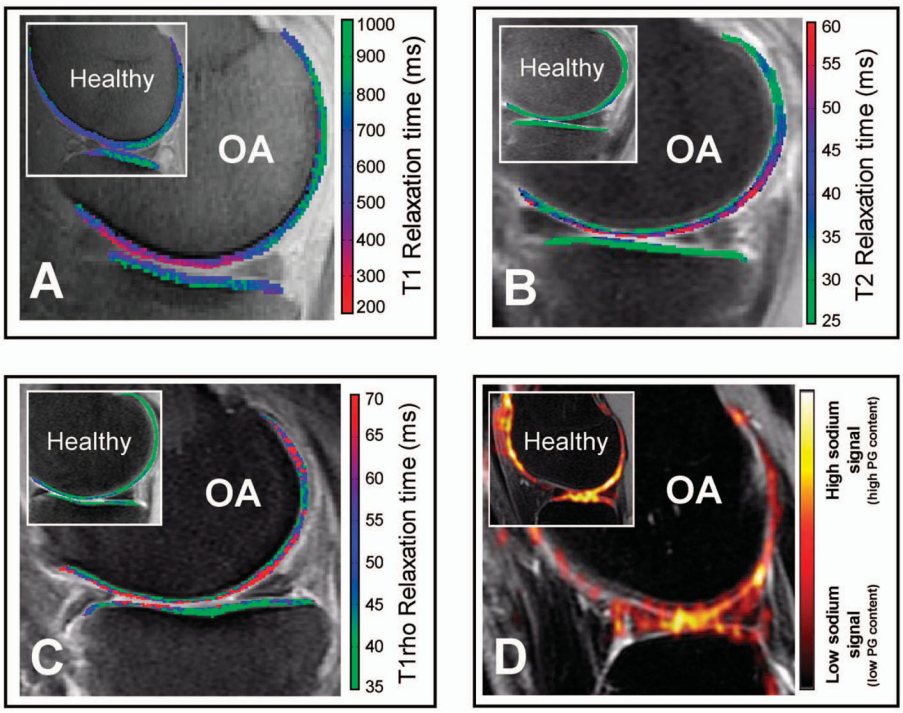

Figure 2.

Delayed gadolinium-enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC), T2 mapping, T1rho mapping, and sodium imaging differentiate between healthy and early-stage knee osteoarthritis (OA). Sagittal slices through the center of the medial or lateral tibiofemoral compartment of knee OA patients and healthy volunteers (**insets**) acquired using different quantitative MRI techniques (all images acquired in different subjects). None of the early OA patients showed clear abnormalities on the conventional MRI sequences (not shown). **A**, dGEMRIC color map shows a clear decrease in T1 relaxation times (purple/red) in early OA, representing loss of glycosaminoglycans. **B**, T2 mapping demonstrates increased T2 relaxation times (blue/purple/red) in early OA due to disorganization of the collagen matrix and increase in water content. **C**, T1rho mapping shows increased T1rho relaxation times (red) in a patient with moderate knee OA. **D**, Sodium MRI detects less sodium signal in OA compared to healthy knee cartilage (**inset**). PG = proteoglycan. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22316/abstract.

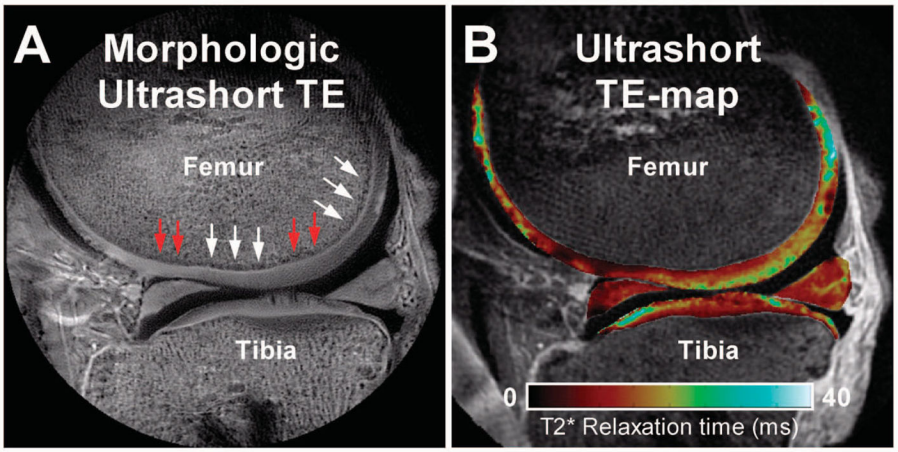

Figure 3.

Morphologic and quantitative ultrashort echo time (TE) images of the knee. Ultrashort TE morphologic (**A**) and quantitative T2* (**B**) magnetic resonance images of a cadaveric knee (male donor, age 77 years). Note that the deepest layer of articular cartilage is clearly visible as a line of high signal intensity (**A**, **white arrows**), along with focal areas of diminished signal intensity (**A**, **red arrows**) that may suggest abnormality of the deep region. (Courtesy of Christine Chung, University of California, San Diego).

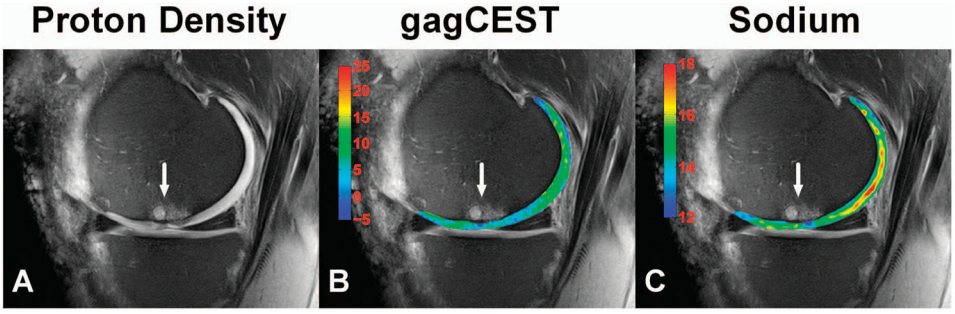

Figure 4.

Glycosaminoglycans (GAGs)–specific chemical exchange saturation transfer (gagCEST) and sodium magnetic resonance imaging (MRI) to followup cartilage repair. Proton density (**A**), gagCEST (**B**), and sodium (**C**) MRIs acquired at 7T of a patient 8.7 years after autologous osteochondral transplantation (**white arrow**). The color overlay in (**B**) represents the gagCEST asymmetries in percentages (the lower the values, the less GAGs are present in the cartilage). The color overlay in (**C**) represents the sodium signal-to-noise ratio values (the lower the values, the less GAGs are present in the cartilage). The transplantation region (**white arrow**) clearly contains less GAGs compared to the posterior femoral cartilage (**B** and **C**). The CEST image (**B**) has a relatively high spatial resolution compared to the sodium image (**C**), which makes the technique promising as an outcome measure for cartilage GAG content in future research. (Courtesy of Benjamin Schmitt and Siegfried Trattnig, Medical University of Vienna, MR Center of Excellence, Vienna, Austria [154]).

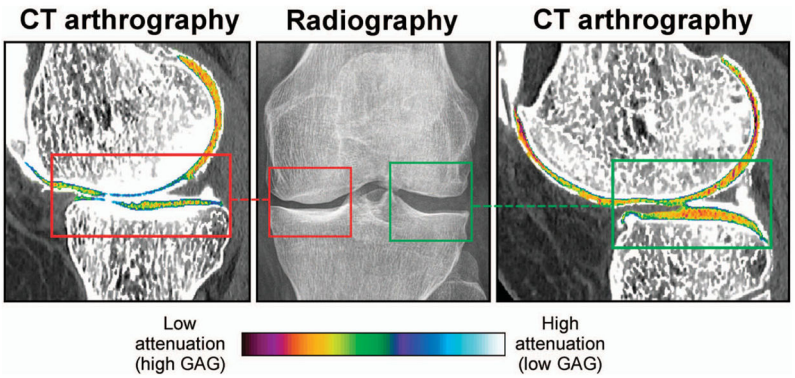

Figure 5.

Quantitative computed tomography (CT) arthrography detects Glycosaminoglycans (GAGs) reduction in osteoarthritis. Representative image of a knee with medial joint space narrowing (**red box**, middle panel) and a normal lateral joint space (**green box**, middle panel). CT arthrography clearly shows higher radiographic attenuation values, indicating less GAGs in the medial knee compartment (**red box**, left panel) compared to the lateral tibiofemoral compartment (**green box**, right panel) (34). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22316/abstract.

Table 1

Outcome measures, clinically relevant biochemical correlates, reported ranges for healthy and OA-diseased cartilage in literature, and advantages and disadvantages per quantitative imaging technique*

Technique	Clinically relevant biochemical correlate	Outcome measure	Reported outcome range†		References, reported outcome range	Advantage	Disadvantage
			Healthy cartilage	OA cartilage‡			
dGEMRIC§	GAG	T1 relaxation time	600–800 ms	300–600 ms	52, 57, 59, 64, 169, 172	Currently best validated indirect GAG measurement	Use of contrast agent with associated risks Long examination time
T2 mapping	Collagen content and orientation	T2* relaxation time	30–45 ms	40–60 ms	92, 98, 99, 105, 173–175	Correlation with collagen content and orientation without need for exogenous contrast agent	May possibly detect degenerative cartilage changes at a later stage than GAG specific techniques Magic angle effect
T1rho mapping	PG/GAG	T1rho relaxation time	30–50 ms	40–80 ms	92, 98, 99, 174, 176	Advocated to be sensitive to PG depletion without need for exogenous contrast agent	Exact biochemical correlate still controversial High RF power required, thus limited by SAR
Ultrashort TE	Collagen content and orientation	T2* relaxation time	20–30 ms	NR	148, 177	Enables visualization of deep cartilage layers, osteochondral junction, and subchondral bone	Long scan times Several technical MRI challenges
gagCEST#	GAG	CEST asymmetry	4–15%	NR	152–154	Direct measure of GAG content without need for exogenous contrast agent	Technically complex Requires high magnetic field strength Sophisticated postprocessing tools required
Sodium MRI¶	GAG	Sodium (^{23}NA) signal intensity	10–35	NR	152, 154, 162, 178	Strong correlation with GAG content without need for exogenous contrast agent	Demanding MRI hardware requirements: (ultra) high field scanners, special RF coils Limited spatial resolution Long examination time
CT arthrography	GAG	X-ray attenuation	NR	NR	NA	Enables quantitative cartilage imaging in subjects with MRI contra-indications Short examination time (seconds instead of minutes) Detailed information on subchondral bone	Use of intraarticular contrast with associated risks Use of ionizing radiation Limited information on other soft tissues

*OA = osteoarthritis; dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging (MRI) of cartilage; GAG = glycosaminoglycan; PG = proteoglycan; RF = radio frequency; SAR = specific absorption rate; TE = time to echo; NR = range not reported for in vivo human knee cartilage in the published literature; gagCEST = GAG-specific chemical exchange saturation transfer; CT = computed tomography; NA = not applicable.

†Ranges are reported for human in vivo (patellar, femoral, or tibial plateau) cartilage of the knee examined with 3.0T MRI equipment unless indicated otherwise.

‡All stages of OA according to Kellgren and Lawrence grading (179) were included in the OA cartilage outcome range.

[§] Reported dGEMRIC outcome range for double dose (0.2 mmole/kg) intravenous contrast agent administration.

[¶] Reported outcome range acquired at 7.0T instead of 3.0T.