Cartilage – Imaging Techniques – Clinical Applications

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I. T2-Mapping

Numerous clinical studies have used T2 mapping, but studies to evaluate the association of cartilage T2 measurements with symptoms are sparse. Only one study assessed cartilage T2 values in a matched cohort with and without knee pain; it found elevated T2 values in subjects with knee pain [1]. On the other hand the association of T2 values with risk factors for OA including age, gender, obesity, and malalignment has been extensively studied. Mosher et al. demonstrated an association of elevated T2 values in superficial cartilage layers with age, suggesting that initial degenerative changes may occur at the articular surface with aging [2]. A study comparing differences in T2 values between healthy men and women found no differences between genders [3]. A study of 267 subjects from the Osteoarthritis Initiative found higher knee cartilage T2 values in obese subjects compared to those with normal weight [4]. Serebrakian and colleagues found a decrease in body mass index of 10% or more to be associated with slower progression of cartilage T2 values over four years in the knees of subjects with risk factors for OA [5].
Longitudinal studies of the effect of knee malalignment on cartilage T2 values are lacking. One cross-sectional study, however, compared the knees of 12 subjects with varus and 12 with valgus malalignment, and found an association of increased cartilage T2 with varus malalignment in the medial compartment [6]. The association of physical activity with cartilage degeneration remains controversial and only a few studies have assessed the relationship using T2 mapping. Acute loading of the knee after physical exercise results in decreased T2 values in the weight bearing femur and tibia, likely secondary to water mobility [7,8]. Studies examining long-term effects of physical activity have found higher levels of exercise to be associated with higher cartilage T2 values [9, 10]. In a longitudinal study that assessed activity based on a physical activity scale for the elderly (PASE), increased cartilage T2 value progression was seen in those with high levels of physical activity as well as those with very low physical activity levels. This suggests that sedentary lifestyle and high-loading both effect cartilage integrity [11]. Using arthroscopy as the reference, one recent study suggested that the addition of a T2 mapping sequence to a routine MRI protocol at 3.0T improved sensitivity in the detection of cartilage lesions within the knee joint with only a small reduction in specificity [12].

II. T2* Mapping

Clinical studies using T2* mapping to study osteoarthritis are scarce. T2* mapping shows decreased values in hip cartilage of subjects with femoro-acetabular impingement [13] and also in those with a slipped capital femoral epiphysis [14]. This decrease in T2* values has also been shown to correlate with morphological cartilage damage. In a study of symptomatic and asymptomatic subjects with a cavovarus malalignment of the ankle, Krause et al. performed T2* mapping on the ankles and then graded them morphologically using the American Orthopaedic Foot and Ankle Society (AOFAS) score [15]. T2* values in symptomatic patients were higher than those in asymptomatic volunteers.

III. T1rho Mapping

Regatte et al. have suggested that T1rho relaxation mapping is a sensitive imaging marker for quantitative monitoring of macromolecules in early OA [16]. T1rho

relaxation time has been shown to be longer in cartilage with advanced degeneration than in cartilage with intermediate degeneration [17]. Although T1rho value changes are correlated with proteoglycan loss in vitro [18], other studies have suggested that T1rho values may not be specific to any one inherent tissue parameter [19]. There is evidence that other factors, including collagen fiber orientation and the concentration of other macromolecules, also contribute to changes in T1rho values [20]. T1rho imaging has been suggested to be more sensitive than T2 mapping for differentiating between normal cartilage and early-stage OA [21]. A recent study by Wang et al. compared parallel changes of quantitative T2, T1rho, and dGEMRIC mapping of human cartilage and suggested that T1rho and dGEMRIC mapping seem to be more sensitive in detecting early stages of cartilage degeneration than quantitative T2 [22]. A recent study by Thuillier et al. showed that the T1rho technique was able to differentiate subjects with patellofemoral pain from controls, but T2 values were not [23]. However, studies by Li et al. have shown that T2 and T1rho values show different spatial distributions and may provide complementary information [24]. A few studies have examined the associations between T1rho values and OA risk factors. A study by Wang et al. suggested some degree of association between knee alignment and subregional T1rho values of femorotibial cartilage in patients with clinical OA [25]. They found significantly higher T1rho values in the medial femoral cartilage subregion in the varus group than in any other cartilage subregions in the valgus group. A study of active subjects by Stahl et al. found that T1rho could distinguish subjects with focal cartilage lesions from those without lesions, albeit the added value of compositional assessment of focal morphologically detectable lesions remains unclear. Souza et al. observed significant elevations in T1rho values of the adjacent compartment (medial tibia) and medial meniscus in subjects with medial femoral cartilage lesions [26]. A study by Zarins et al. correlated meniscal damage with cartilage degeneration, using both T2 and T1rho measurements [27]. Bolbos et al. demonstrated injury related changes in cartilage and meniscal biochemical composition using T1rho mapping in patients with acute ACL injuries [28]. The T1rho mapping technique has been shown to non-invasively detect cartilage pathology in knees with injured ACL [29]. Li et al. have shown that T1rho can detect the changes in the cartilage matrix in ACL-reconstructed knees as early as one year after reconstruction [30].

IV. dGEMRIC Mapping

dGEMRIC is sensitive to cartilage proteoglycan content and may predict the 297 development of OA [31]. It was recently demonstrated that T1Gd values in medial tibiofemoral compartments decrease as the radiographic Kellgren-Lawrence grade increases [32]. Prescribed immobilization after injury, of only six weeks, has been shown to result in biochemical changes in the cartilage measureable by dGEMRIC with a mean decrease seen in T1 relaxation time (T1Gd) seen at four months, which persisted for up to a year [33]. In a longitudinal study, Owman et al. found that low baseline T1Gd using dGEMRIC in medial and lateral femoral cartilage was associated with a higher grade of joint space narrowing after 11 years, and also with development of osteophytes [34]. A study by Crema et al. found high-grade medial meniscal damage to be associated with low T1Gd times in the medial tibiofemoral compartment [35]. Lattanzi et al. recently demonstrated that dGEMRIC was accurate in detecting, at the hip, cartilage damage due to femoroacetabular impingement [36]. In an earlier study, Kim et al. also showed that dGEMRIC index was significantly different in subgroups with mild, moderate, and severe grades of hip dysplasia [37], which suggests the ability of dGEMRIC to detect varying cartilage

degeneration among these groups. In a study of 111 obese adults, dGEMRIC showed that weight loss over the course of a year resulted in increased cartilage proteoglycan content [38]. A recently published study evaluated articular cartilage using dGEMRIC after viscosupplementation with hyaluronic acid in patients with early knee OA [39]. The study found no change in the structural composition of cartilage after 14 weeks, even though symptomatic improvement was reported. However, another recent study showed that a decrease in T1Gd values over 318 predicted an increase in cartilage thickness in the same tibiofemoral compartment after two years, mainly in middle-aged women with no radiographic OA or early 320 radiographic OA [40]. The authors suggested that such an association might occur in the early stages of degeneration when swelling of cartilage (with increased thickness) is seen. To date, there is no strong evidence that changes in dGEMRIC over time predict progression of cartilage loss.

V. Sodium Imaging

Sodium imaging correlates with the fixed charge density and GAG content in cartilage [41] and therefore may also be used in early detection of OA. Clinical studies using sodium MRI, however, are limited. A feasibility study by Wheaton et al [42] used sodium imaging to compare the cartilage of healthy subjects with subjects with symptoms of early OA. They found a higher mean fixed-charge density in the healthy individuals. The symptomatic subjects had focal regions of decreased fixed charge density, with mean values ranging from -108 to -144 mmol/L, indicative of proteoglycan loss [42]. Madelin et al reported the reproducibility and repeatability of sodium quantification in cartilage in vivo using intraday and interday acquisitions at 3T and 7T, with a radial 3D sequence, with and without fluid suppression [43]. No significant intermagnet, intersequence, intraday, or interday differences were observed in the coefficients of variation. A recently described sodium quantification technique using inversion recovery wide-band uniform rate and smooth truncation (IR-WURST) gave values that were closer to those reported in the literature for healthy cartilage (220–310mM) than the values from radial 3D. A recent study [44] also reported that the sodium concentration in both healthy and OA knees at 7T imaging with fluid suppressed sodium MRI can be used for detection of osteoarthritis with 82% sensitivity, 74% specificity and 78% accuracy.

VI. DWI and gagCEST

Diffusion imaging may supplement other quantitative techniques for evaluating cartilage, but clinical studies that use the technique are scarce. Recent studies to determine the feasibility of in vivo diffusion tensor imaging have shown promising results [45, 46, 47]. Diffusion tensor imaging showed excellent reproducibility and may be able to differentiate healthy from OA subjects [47]. Clinical studies examining the potential role of gagCEST in assessment of OA related cartilage degeneration are lacking. Feasibility studies using in vivo gagCEST have shown gagCEST MRI to be sensitive to GAG levels in the cartilage [48]. In addition, the method allows one to clearly demarcate glycosaminoglycan measurements from cartilage and synovial fluid regions [49]. A recent study by Rehnitz et al. prospectively compared gagCEST with dGEMRIC and T2 [50]. The authors of this study reported that gagCEST was non-inferior in distinguishing healthy from damaged cartilage when compared to dGEMRIC and T2 mapping. Further studies are needed to establish the potential value of this technique in assessment of OA related cartilage degeneration.

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COMPOSITIONAL MRI ASSESSMENT OF REPAIR TISSUE

There is extensive literature on quantitative MRI measurements applied to the study cartilage degeneration. Fewer studies have investigated transplanted or regenerative cartilage repair tissue.

1) Marrow Stimulation

T2 relaxation times of repair tissue after microfracture are lower in the repair tissue than in healthy cartilage, possibly due to fibrous/fibrocartilaginous repair tissue (103, 142-146). Additionally, there is no zonal distribution between the deep and superficial articular cartilage layers, reflecting the disorganized collagen architecture that develops following microfracture. A recent feasibility study compared T2 and T2* mapping in cartilage repair tissue following microfracture against non-operated cartilage and found that T2* values were consistently lower than T2 measurements, likely due to the greater sensitivity of T2* to magnetic susceptibility and inhomogeneity (118). T2* mapping was able to differentiate between normal and repair tissue, with lower values seen in repair tissue. Only healthy cartilage demonstrated a zonal distribution of T2 and T2* values, with both values increasing from the deep to superficial layers.

T1rho and T2 quantification have been studied for longitudinal evaluation of microfracture repair tissue. Longer T1 rho and T2 values were found in repair tissue compared to native cartilage 3-6 months after surgery (146, 147). After one year, however, the difference between native cartilage and repair tissue decreased and remained significant only for the T1rho measurements. A zonal distribution with higher T1rho and T2 values in the superficial layers of repair tissue was demonstrated in this study, with the difference maintained after one year only with T1rho measurements. The authors concluded that T1rho might complement T2 relaxation time in assessment of repair tissue maturation (146, 147).

Microfracture repair tissue has been shown to have a significantly lower MTC ratio compared to native cartilage (145). In a dGEMRIC study comparing microfracture and MACT, a significantly higher relative deltaR1 was found in microfracture repair tissue than in MACT suggesting that the GAG content is lower in the microfracture fibrocartilaginous repair tissue (148).

2. Osteochondral Grafting

Only a few reports have evaluated compositional MRI for assessment of osteochondral auto- and allografts. A long-term study of clinical and imaging outcomes after autologous osteochondral transplantation using morphological MRI, T2 maps, gagCEST and sodium imaging found that the only significant correlation was between T2-mapping and clinical outcomes at 7.9 years (149).
A case report of an ex-vivo evaluation of a single autologous osteochondral transfer plug compared T2 maps, dGEMRIC and MTC (150). Higher T2 values were found in the middle and deep layers of the adjacent native cartilage anterior to the graft than in the autograft cartilage. T2 measurements in the superficial and middle layers of the posterior native cartilage were shorter than in the grafted plug. Similarly MTC and dGEMRIC index measurements depended on depth, location, and pathology that were consistent with measurements reported in the literature for articular cartilage. However, the authors suggested caution when interpreting quantitative MRI measurements in formalin-fixed specimens (149).
A canine study comparing auto- and allografting showed no difference in T2s of the two types of grafts at three and six months after surgery (151). An equine study comparing cartilage T2 maps following microfracture and autologous osteochondral transfer showed that the depth-wise stratification of T2 values in the osteochondral grafts correlated with an organized collagen microstructure, while the disorganized microfracture tissue showed no stratification (152).

3) ACI and MACT
Following MACT, full thickness cartilage T2 values were greater than native cartilage during the first year but then returned to normal (153, 154). About one year after surgery, zonal variation of MACT repair tissue T2 values was similar to that of native cartilage. This has been interpreted as an indication of reorganization of the collagen microstructure. T2 mapping has also been able to differentiate between MACT with collagen-based and hyluronan-based scaffolds up to two years after repair (155).
Maturation of ACI repair tissue has also been demonstrated by dGEMRIC, with a lower index in early postoperative tissue that increased to values similar to native cartilage after one year (156). The authors concluded that the time-dependent changes indicate increasing ECM proteoglycans as the repair tissue matures. A dGEMRIC study comparing MACT and microfracture repair tissue using dGEMRIC found that the MACT repair tissue had a higher dGEMRIC index, presumably from higher ECM proteoglycan content (157).
Sodium imaging has been used to differentiate between normal articular cartilage and MACT repair tissue (158). In this particular study, sodium imaging correlated well with dGEMRIC following MACT, demonstrating that both methods are GAG specific. Using sodium imaging as a reference method, gagCEST could differentiate between repair tissue and healthy cartilage in patients after MACT (159).
A pilot study that evaluated microfracture and MACT using sodium imaging found higher GAG content after MACT, suggesting better quality repair tissue (160).

Abstract
Osteoarthritis (OA), a leading cause of disability, affects 27 million people in the United States and its prevalence is rising along with the rise in obesity. So far, attempts to develop disease-modifying OA drugs have been unsuccessful. This may be partly due to antiquated imaging outcome measures such as radiography, which are still endorsed by regulatory agencies such as the United States Food and Drug Administration for use in clinical trials. Morphological magnetic resonance imaging (MRI) allows unparalleled multi-feature assessment of the OA joint. Furthermore,

advanced MRI techniques also enable evaluation of the biochemical or ultrastructural composition of articular cartilage relevant to OA research. These compositional MRI techniques have the potential to supplement clinical MRI sequences in identifying cartilage degeneration at an earlier stage than is possible today using morphologic sequences only. The purpose of this narrative review is to describe compositional MRI techniques for cartilage evaluation, which include T2 mapping, T2* Mapping, T1 rho, dGEMRIC, gagCEST, sodium imaging and diffusion weighted imaging. We also reviewed relevant clinical studies that have utilized these techniques for the study of OA. The different techniques are complementary. Some focus on isotropy or the collagen network (e.g. T2 mapping and T1rho) and others are more specific in regard to tissue composition, e.g. gagCEST or dGEMRIC that convey information on the GAG concentration. The application and feasibility of these techniques is also discussed, as they will play an important role in implementation in larger clinical trials and eventually clinical practice.

Cartilage injuries are common, especially in athletes. As these injuries frequently affect young patients, and they have the potential to progress to osteoarthritis, treatment to alleviate symptoms and delay joint degeneration is warranted. A number of surgical techniques are available to treat focal chondral defects including marrow stimulation, osteochondral auto- and allografting, and autologous chondrocyte implantation. Although arthroscopy is considered the gold standard for evaluation of cartilage pre- and postrepair, it is invasive with associated morbidity and cannot adequately assess the deep cartilage layer and underlying bone. Magnetic resonance imaging (MRI) provides unparalleled non-invasive assessment of the repair site and all other joint tissues. MRI observation of cartilage repair tissue (MOCART) is a well-established semi-quantitative scoring system for repair tissue and the MRI osteoarthritis knee score (MOAKS) is a commonly utilized scoring system for grading knee osteoarthritis features. The cartilage repair osteoarthritis knee score (CROAKS) optimizes comprehensive morphological assessment of the joint after cartilage repair by combining features of MOCART and MOAKS. Furthermore, advanced compositional MRI sequences including T2, T2* and T1rho quantification, and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), diffusion-weighted imaging and diffusion tensor imaging, sodium imaging, magnetization transfer contrast (MTC) and glycosaminoglycan chemical exchange saturation transfer imaging (gagCEST) are available for biochemical assessment. These quantitative MRI techniques assess collagen content and orientation, water content and glycosaminoglycan (GAG)/proteoglycan content in the repair tissue as it matures, and also within the non-operated “native” cartilage. This review discusses the principles of state-of-the-art morphological and compositional MRI techniques for imaging of cartilage repair and their application to longitudinal studies.