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Clinical Optical Coherence Tomography of Early Articular Cartilage Degeneration in Patients With Degenerative Meniscal Tears

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Objective. **Quantitative and nondestructive methods for clinical diagnosis and staging of articular cartilage degeneration are important to the evaluation of potential disease-modifying treatments in osteoarthritis (OA). Optical coherence tomography (OCT) is a novel imaging technology that can generate microscopic-resolution cross-sectional images of articular cartilage in near real-time. This study tested the hypotheses that OCT can be used clinically to identify early cartilage degeneration and that OCT findings correlate with magnetic resonance imaging (MRI) T2 values and arthroscopy results.**

Methods. **Patients undergoing arthroscopy for degenerative meniscal tears were recruited under Institutional Review Board–approved protocols. Thirty consecutive subjects completing preoperative 3.0T MRI, arthroscopy, and intraoperative OCT comprised the study group. Qualitative and quantitative OCT results and MRI T2 values were compared with modified Outerbridge cartilage degeneration scores (0–4 scale) assigned at arthroscopy.**

Results. **Arthroscopic grades showed cartilage abnormality in 23 of the 30 patients. OCT grades were abnormal in 28 of the 30 patients. Both qualitative and quantitative OCT strongly correlated with the arthroscopy results ($P = 0.004$ and $P = 0.0002$, respectively, by Kruskal-Wallis test). Neither the superficial nor the deep cartilage T2 values correlated with the arthroscopy results. The quantitative OCT results correlated with the T2 values in the superficial cartilage (Pearson's $r = 0.39$, $P = 0.03$).**

Conclusion. **These data show that OCT can be used clinically to provide qualitative and quantitative assessments of early articular cartilage degeneration that strongly correlate with arthroscopy results. The correlation between the quantitative OCT values and T2 values for the superficial cartilage further supports the utility of OCT as a clinical research tool, providing quantifiable microscopic resolution data on the articular cartilage structure. New technologies for nondestructive quantitative assessment of human articular cartilage degeneration may facilitate the development of strategies to delay or prevent the onset of OA.**

Osteoarthritis (OA) is reaching epidemic proportions as the population ages (1). Posttraumatic OA occurs more frequently in younger age groups during the prime work years, rendering OA a leading cause of disability worldwide (2). While OA is of multifactorial etiology and eventually involves the entire joint, the central pathologic feature has traditionally been attributed to the progressive loss of articular cartilage (3). Consequently, there is great clinical need for early diagnosis and treatment of cartilage degenerative processes.

Historically, OA has been diagnosed radiographically based on the characteristic bone changes (representing the "osteo" portion of the name) that occur at advanced stages of cartilage loss and degeneration (4). When the cartilage is already gone, the disease is too advanced for efforts to protect or restore the articular cartilage. There currently are no Food and Drug Administration–approved disease-modifying OA drugs.

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Arthroscopy is the current clinical standard for evaluating pre-OA cartilage lesions, which are also referred to as chondrosis. These lesions do not yet involve bone and frequently are not visible by radiographic examination (5,6). These arthroscopic changes begin with the subjective identification of cartilage "softening" by palpation, followed by superficial surface fibrillations that progress to involve the full thickness of the cartilage and then the underlying bone (7). There is increasing evidence that these descriptions pertain to a continuum of cartilage loss culminating years later in the characteristic bone and joint changes of OA (8).

Conventional magnetic resonance imaging (MRI) has been shown to be useful in identifying later stages of chondrosis manifested by changes in cartilage morphology, consisting of partial-thickness and full-thickness fissuring and defects, but conventional MRI cannot reliably differentiate between healthy and diseased cartilage with intact articular surfaces (9). Newer quantitative MRI evaluations, such as T2 mapping of articular cartilage, have been shown to be dependent on collagen orientation and tissue hydration (10–12). Unlike standard MRI, T2 mapping can provide quantitative information about subsurface articular cartilage structure and biochemical integrity (13).

Barriers to the development and assessment of chondroprotective and disease-modifying agents include the identification of cartilage disease before the development of irreversible changes. The earliest signs of cartilage injury and degeneration include potentially reversible metabolic perturbations accompanied by microstructural changes occurring prior to visible breakdown of the articular surface (14). While these changes can be detected in the laboratory through histologic, biochemical, and metabolic studies of tissue biopsy samples, they can elude detection by conventional arthroscopic surface inspection and probing or structural MRI (15–19). These changes, therefore, are not currently identifiable clinically, except perhaps by histopathologic assessment (20), which is not practical for early diagnosis because it requires removal and destruction of the cartilage being examined.

Optical coherence tomography (OCT) is a novel, nondestructive imaging technology that can be incorporated into arthroscopes to generate cross-sectional images of articular cartilage in near real-time and at resolutions (10–20 μm) that are comparable to low-power histologic assessment (21–24). OCT has also been shown to be sensitive to changes in collagen architecture resulting from both acute trauma and degeneration (24). Recent studies have shown that OCT can identify changes in cartilage birefringence associated with potentially reversible metabolic changes that have been implicated in the pathogenesis of OA (16). This study was performed to test the hypotheses that OCT can be used clinically to identify early cartilage degeneration and that OCT findings correlate with MRI T2 values and conventional arthroscopy results.

PATIENTS AND METHODS

Human subjects. Patients in whom arthroscopic meniscal surgery was indicated provided their informed consent for study, according to the Institutional Review Board–approved protocol. The primary diagnosis of degenerative meniscal tear was defined by 2 criteria: having a complex, horizontal, or radial meniscal tear pattern on clinical MRI scan, and having either normal or near-normal tibiofemoral joint spaces (grade 0 or 1) on standing anteroposterior and 45° flexed posteroanterior radiographs (25).

Thirty consecutive patients undergoing arthroscopic treatment for degenerative meniscal tears who completed a preoperative 3.0T quantitative MRI examination, a conventional arthroscopic examination, and an arthroscopic OCT examination comprised the sample for this study. There were 13 women and 17 men, with a mean ± SD age of 42.5 ± 13.8 years (range 18–68 years) and mean ± SD body mass index of 28.0 ± 5.9 (range 20–43).

MRI assessment. Within 1 month prior to surgery, a preoperative-study MRI was performed with a Siemens whole-body Magnetom Trio 3T MR imager, using the National Institutes of Health–sponsored Osteoarthritis Initiative (OAI) sequences and scanner (www.oai.ucsf.edu) and a standard extremity coil. Multislice sagittal 2-dimensional (2-D) T2 mapping images were acquired using a fast spin-echo sequence with 7 echo images (TEs) ranging from 10 msec to 80 msec and a repetition time (TR) of 2,700 msec. The 2-D images were collected in a 12-cm field of view (FOV) with a 384 × 384–pixel matrix for 313 × 313–μm in-plane resolution. A total of 27–30 slices (3 mm thick) were collected. The bandwidth was 250 Hz/pixel, and the scan time was ~10 minutes.

Prior to T2 curve-fitting, the TE images were downsampled using cubic interpolation with MatLab (MathWorks) to increase the signal-to-noise ratio, creating an effective resolution of 416 × 416 μm in-plane. T2 maps were generated for a single section from the center of the medial femoral condyle using MRIMapper software (Beth Israel Deaconess and Massachusetts Institute of Technology; 2006) running on a MatLab platform. The shortest echo image (TE 10 msec) was not included in the T2 curve-fitting routine. A small, full-thickness region of interest (ROI) in the center of the medial femoral condyle was manually segmented for each section mapped. These ROIs were further subdivided into 2 approximately equal sections to examine zonal T2 variations: a deep zone (extending from the subchondral bone to the center of the tissue to encompass the bottom half of the tissue thickness) and a superficial zone (extending from the center of the tissue

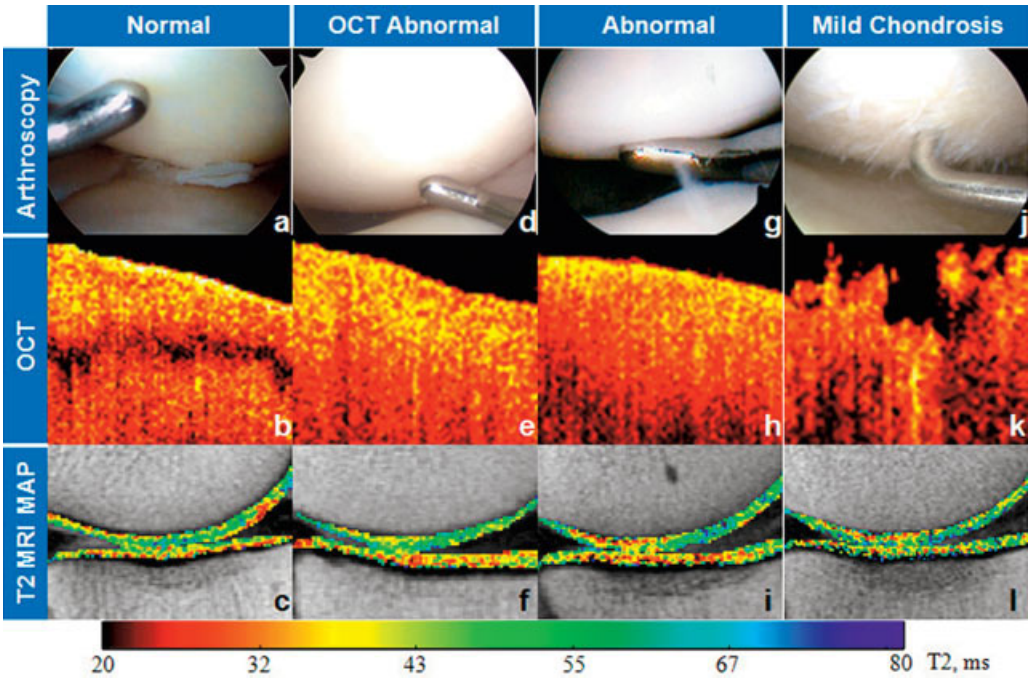

Figure 1. Representative images obtained during arthroscopy, optical coherence tomography (OCT), and magnetic resonance imaging (MRI) T2 mapping. **a–c,** Arthroscopically firm (**a**), OCT with birefringence (**b**), and MRI T2 map showing 54 ± 9 msec (mean ± SD) for superficial tissue and 49 ± 11 msec for deep tissue (**c**). **d–f,** Arthroscopically firm (**d**), OCT without birefringence (**e**), and MRI T2 map showing 55 ± 9 msec for superficial tissue and 45 ± 8 msec for deep tissue (**f**). **g–i,** Arthroscopically softened (**g**), OCT without birefringence (**h**), and MRI T2 map showing 46 ± 11 msec for superficial tissue and 43 ± 13 msec for deep tissue (**i**). **j–l,** Arthroscopically fissured (**j**), OCT fissured (**k**), and MRI T2 map showing 55 ± 9 msec for superficial tissue and 45 ± 8 msec for deep tissue (**l**).

to the articular surface). The average T2 values for the superficial and deep zone ROIs were recorded.

Arthroscopic evaluations. During surgery, targeted standard arthroscopic and arthroscopic OCT examinations were conducted on the study areas in the central weight-bearing region of the medial femoral condyle. Visual landmarks, consisting of the top of the notch, the posterior border of the condyle when the knee is flexed at 90°, and the medial and lateral borders of the condyle, were used to define the central weight-bearing region and the midsagittal plane of the medial femoral condyle. Arthroscopic grades were assigned to the area by the treating surgeon (CRC), using a modified Outerbridge scale (scored on a scale of 0–4, where 0 = firm cartilage, 1 = softening of the cartilage, 2 = partial-thickness defect with superficial fissures, 3 = fissuring to subchondral bone, and 4 = exposed subchondral bone). The arthroscopic examination and grading were performed at the beginning of the case assessment and were recorded prior to OCT imaging.

Arthroscopic OCT images were acquired using a handheld arthroscopic probe fitted with the sample arm of a fiberoptic OCT imager (Imalux Niris Imaging System). The light source consisted of a super luminescent diode with a center wavelength of 1,310 nm and a spectral bandwidth of 55 nm. The optical power of the probe was <6 mW and generated echographs of infrared light with horizontal and depth resolutions of 10–20 μm. The OCT probe was capable of generating cross-sectional images measuring 2 mm wide by 1.5 mm deep of the articular cartilage directly in line with the face of the probe. Clinical imaging of the weight-bearing region of the medial femoral condyle was performed by advancing the probe through a standard anteromedial knee arthroscopy portal.

Cartilage OCT imaging was performed according to published methods (16). Briefly, the study areas were scanned by sequentially rotating the handheld OCT probe through 4 different radial orientations at 45° apart. The resulting image series constituted the OCT examination for each study area.

Grading of OCT images. OCT images were randomized for blinded grading by 2 independent observers (CRC and SB) weeks to months following image acquisition. OCT images were graded on a scale of 0–3 according to the following criteria. Tissue demonstrating clearly distinguishable banding patterns (Figure 1b) in at least 1 radial orientation was classified as exhibiting OCT form birefringence (OCT grade 0). Tissue with partial banding in any of the 4 orientations was classified as exhibiting intermediate OCT form birefringence (OCT grade 1). Tissue that did not demonstrate the characteristic multilaminar pattern in any of the 4 orientations was classified as lacking OCT form birefringence (OCT grade 2).

Tissue with surface incongruity was classified as exhibiting an irregular articular surface (OCT grade 3).

Quantitative analysis of OCT images. Custom image analysis software was used to automatically extract image feature data from the OCT images (26). The automated feature-generation process consisted of 3 main steps. First, cartilage tissue regions were segmented from the images. Second, a nonlinear smoother was used to enhance the edge structures. Third, edge measurements that assess the intensity variations in the cartilage were made. Variation statistics were used to produce an automatic scoring for each OCT image.

Details of the feature-generation process were as follows. First, the total variation (27) edge-preserving filtering function was applied to each image using 2 scales: a fine scale ($\lambda = 0.05$; removing only high-frequency noise) and a coarser scale ($\lambda = 0.10$; suppressing small local variations, revealing larger-scale intensity trends in the image). Second, using the gradient information in each $\lambda = 0.05$–filtered image, the cartilage interface was detected using the spectral rounding algorithm (26). The area under the interface was taken as the cartilage measurement area. Third, a matched quadrature-pair filter bank (28) was then applied to each $\lambda = 0.10$–smoothed image, measuring the intensity contrasts at multiple scales and orientations. Finally, 2 features were extracted and combined: the average squared-edge intensity over all orientations and the horizontal-edge variance, both of which were restricted to the cartilage measurement area. These statistics were then used to predict the arthroscopic score associated with the sample.

Statistical analysis. Subjective OCT grades, quantitative OCT feature data, and T2 values (superficial and deep) were compared with the surgeon's arthroscopic grade, which was used as the standard. OCT grades, OCT feature data, and T2 values were grouped according to arthroscopic grade, and nonparametric Kruskal-Wallis tests were used to assess the variation of each parameter with the arthroscopic grade. The arthroscopy data were then dichotomized, and post hoc pairwise nonparametric Mann-Whitney tests were used to detect differences between groups. A 2-tailed *t*-test was used to analyze differences in T2 values between superficial and deep zones, as well as to test for quantitative differences between patients with arthroscopic grade 0 tissue and those with arthroscopic grade 1 tissue. Linear regression was used to examine the relationship between T2 relaxation time and OCT numerical feature data. Kruskal-Wallis and Mann-Whitney tests were performed with SPSS software. All other statistical analyses were performed with the Excel program (Microsoft).

RESULTS

The data obtained from arthroscopy, subjective and quantitative OCT, and MRI T2 assessments in each patient are shown in Table 1 and are categorized by arthroscopy grade. Representative images from the arthroscopic, OCT, and MRI T2 procedures are shown in Figure 1.

Arthroscopic findings. Arthroscopic surface imaging and palpation revealed that 50% of the patients (15 of 30) had intact articular surfaces in the central weight-bearing region of the medial femoral condyle. The distribution of the arthroscopic scores (Figure 2) was as follows: 7 patients had grade 0 (firm), 8 had grade 1 (soft), 6 had grade 2 (fissuring of <50% of cartilage thickness), 6 had grade 3 (fissuring of >50% of cartilage thickness), and 3 had grade 4 (exposed bone). The mean ± SD modified Outerbridge score was 1.6 ± 1.3, with a median score of 1.5.

Table 1. Study data, by arthroscopic grade*

		OCT		MRI T2	
Study subject	Arthroscopic grade	Subjective grade	Quantitative feature score	Superficial, msec	Deep, msec
A	0	1	0.76	42	40
B	0	0	0.00	54	49
C	0	2	1.16	52	39
D	0	0	0.00	40	33
E	0	2	0.98	51	33
F	0	2	0.86	55	45
G	0	2	1.29	42	35
H	1	2	1.48	41	32
I	1	2	0.75	36	31
J	1	2	0.95	49	31
K	1	3	1.73	53	40
L	1	1	0.63	41	39
M	1	2	1.61	31	29
N	1	2	1.25	46	43
O	1	2	1.38	43	36
P	2	1	0.73	51	29
Q	2	2	1.89	51	36
R	2	2	1.84	60	33
S	2	3	2.08	49	31
T	2	3	1.88	40	31
U	2	3	1.58	45	39
V	3	2	2.01	51	30
W	3	3	2.45	48	34
X	3	3	3.59	55	42
Y	3	3	4.00	50	36
Z	3	3	3.03	47	41
AA	3	3	3.28	56	36
BB	4	3	3.27	45	37
CC	4	3	3.53	64	46
DD	4	3	2.57	63	46

* OCT = optical coherence tomography; MRI = magnetic resonance imaging.

OCT findings versus arthroscopic findings. The distribution of subjective OCT grades binned (grouped) by arthroscopic grade (Figure 2) revealed that 5 of the 7 patients with arthroscopically firm cartilage (arthroscopic grade 0) were graded as abnormal on OCT (OCT grade >0). Subjective OCT grades increased with increasing arthroscopic grade ($P = 0.004$ by Kruskal-Wallis test) (Figure 3a) and discriminated between tissue with an intact articular surface and tissue with surface defects (arthroscopic grades 0 and 1 versus

arthroscopic grades 2–4; $P = 0.001$ by Mann-Whitney test).

The 2 independent graders agreed on the subjective OCT grade 90% of the time ($\kappa = 0.88$). Subjective OCT grades were not significantly different for firm versus softened tissue with intact articular surfaces (arthroscopic grade 0 versus 1; $P = 0.19$ by Mann-Whitney test). Quantitative feature data were found to vary with arthroscopic grade ($P = 0.0002$ by Kruskal-Wallis test) (Figure 3b) and to discriminate between tissues with an intact surface and tissues with surface defects ($P << 0.001$ by Mann-Whitney test). Quantitative OCT values demonstrated a trend toward differentiating arthroscopically firm cartilage (arthroscopic grade 0) from softened tissue (arthroscopic grade 1) by 2-tailed t-test ($P = 0.057$), but not by the more conservative Mann-Whitney test ($P = 0.12$).

MRI T2 findings versus arthroscopic findings. Neither superficial nor deep MRI T2 values varied significantly with cartilage degeneration as assessed by conventional arthroscopy ($P = 0.11$ and $P = 0.10$, respectively, by Kruskal-Wallis test) (Figure 3c). Comparison of the MRI T2 values in different tissue zones revealed that those in the deep half of articular cartilage (mean ± SD 37 ± 6 msec) were 24% lower than those in the corresponding superficial half of the tissue (48 ± 8 msec) ($P < 0.001$ by t-test) (Figure 4a). T2 values in the superficial cartilage discriminated between tissues with intact articular surfaces (45 ± 7 msec for arthroscopic grades 0 and 1) and those showing surface de-

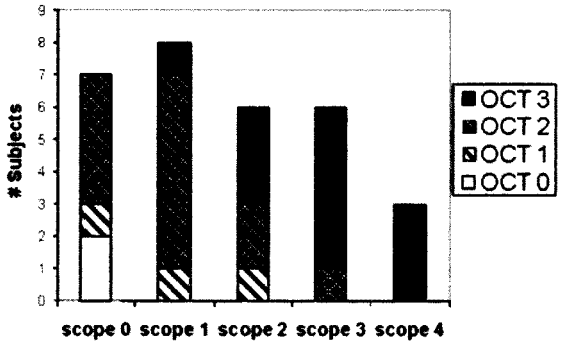

Figure 2. Distribution of the subjective optical coherence tomography (OCT) grades (0–3 scale) according to the arthroscopic (scope) grade (0–4 scale). In this study of patients with degenerative meniscal tears, 5 of 7 patients with arthroscopically firm articular cartilage (arthroscopic grade 0) had abnormal findings on OCT (OCT grade >0). All patients with cartilage that was graded slightly abnormal by arthroscopy (arthroscopic grade 1) had abnormal findings on OCT. The proportion of higher OCT grades, which reflect increasingly abnormal findings, increased with an increasing arthroscopic grade.

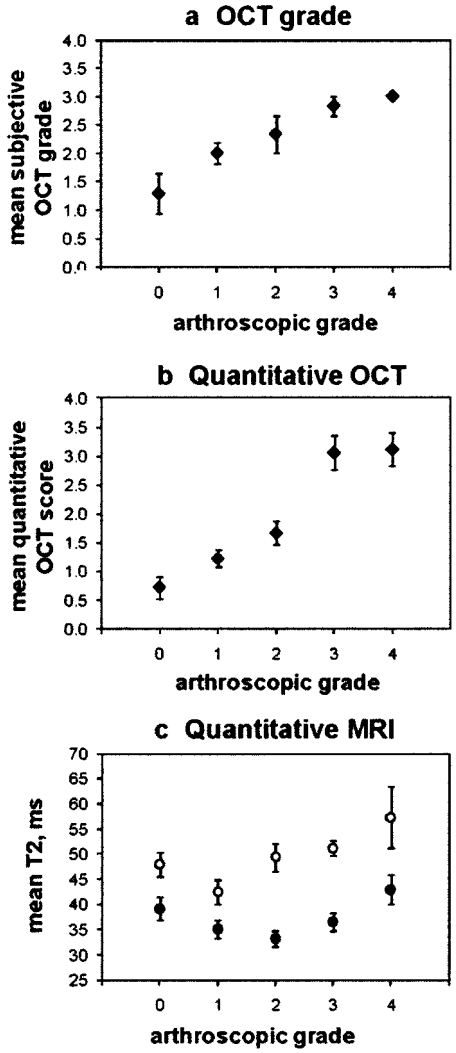

Figure 3. Distribution of optical coherence tomography (OCT) grades (0–3 scale) and magnetic resonance imaging (MRI) T2 grades as compared with the arthroscopic grade as the standard. **a,** Subjective grading of OCT images based on characterization of the birefringence pattern and surface smoothness shows that the OCT grade varies with the arthroscopic grade ($P = 0.004$ by Kruskal-Wallis test). **b,** The mean quantitative OCT values strongly correlate with the arthroscopic disease severity grades ($r = 0.85$, $P = 0.0002$ by Kruskal-Wallis test). **c,** The mean MRI T2 values demonstrate a complex relationship with the arthroscopic grade. The mean MRI T2 values in the superficial region of the cartilage (○) are lowest in softened but intact tissue (arthroscopic grade 1) and increase with increasing degeneration (arthroscopic grades 2–4). The mean T2 values in the superficial region of healthy tissue (arthroscopic grade 0), however, fall in the middle of the range of the observed T2 values in the superficial cartilage. The mean T2 values in the deep region of the cartilage (●) are lowest in tissue with partial-thickness defects and surface fissures. Neither the superficial cartilage nor the deep cartilage T2 values varied significantly with cartilage degeneration as assessed by conventional arthroscopy ($P = 0.11$ and $P = 0.10$, respectively, by Kruskal-Wallis test). Values are the mean ± SEM.

fects in the study location (51 ± 7 msec for arthroscopic grades 2–4) ($P = 0.04$ by Mann-Whitney test) (Figure 4b). MRI T2 values for the deep tissue did not discriminate between these features ($P = 0.87$ by Mann-Whitney test). T2 values in arthroscopically firm cartilage (grade 0) were found in the middle of the range of all observed T2 values, whereas diseased cartilage (arthroscopic grades 1–4) demonstrated increasing T2 values in the superficial cartilage with increasing disease levels. No correlation between deep tissue T2 values and arthroscopic grade was observed.

MRI T2 findings versus OCT findings. Neither superficial nor deep MRI T2 values varied significantly with subjective OCT grade ($P = 0.59$ and $P = 0.46$, respectively, by Kruskal-Wallis test). Quantitative OCT–derived feature scores showed a correlation with superficial MRI T2 values (Figure 5). Pearson's correlation between T2 relaxation times in the superficial cartilage and OCT numerical features was r = 0.39 ($P = 0.03$), whereas Pearson's correlation between the T2 values in the deep cartilage and OCT numerical features was r = 0.13 ($P = 0.50$).

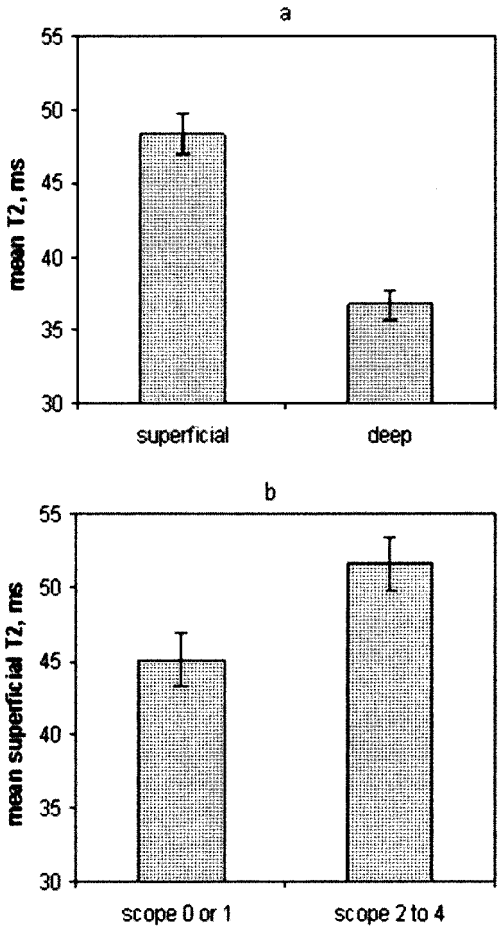

Figure 4. Distribution of magnetic resonance imaging (MRI) T2 mapping data. **a,** The MRI T2 values measured in the superficial half of the cartilage were found to be 24% higher on average than those measured in the deep half of the cartilage ($P << 0.0001$ by *t*-test). **b,** The T2 values in the superficial cartilage discriminated between cartilage with intact articular surfaces and cartilage with surface defects ($P = 0.04$ by Mann-Whitney test). Values are the mean ± SEM.

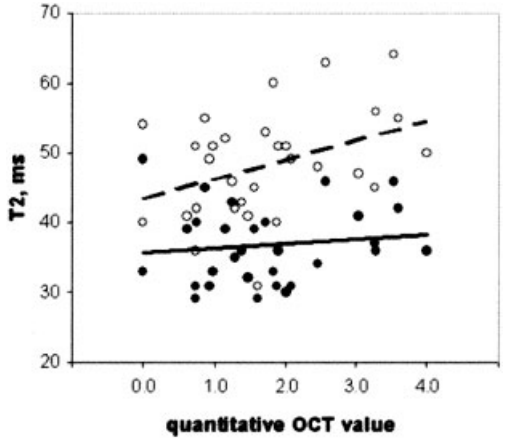

Figure 5. Correlation of magnetic resonance imaging (MRI) T2 values in the superficial cartilage (○) with quantitative optical coherence tomography (OCT) values (Pearson's r = 0.39, $P = 0.03$) (broken line). No correlation is seen between the MRI T2 values in the deep cartilage (●) and the quantitative OCT values (Pearson's r = 0.13, $P = 0.50$) (solid line).

DISCUSSION

The findings of this study show that optical coherence tomography can be used clinically to identify early cartilage degeneration in patients with degenerative meniscal tears and that the OCT results strongly correlate with the results of conventional arthroscopic assessment. Both the qualitative evaluation of OCT birefringence patterns and the quantitative OCT image data showed strong correlations with the grades assigned by conventional arthroscopy. Quantitative OCT values also correlated with superficial MRI T2 map values, providing construct validity, since both modalities generated quantitative cross-sectional information on cartilage subsurface properties. Clinical OCT provided cross-sectional images of a small area of articular cartilage at resolutions comparable to that of low-power microscopy, without the need to damage or remove the tissue. As shown in this study, the ability to obtain quantifiable microscopic resolution data on cartilage subsurface ma-

trix characteristics in the clinical setting is important to advancing the study of early cartilage degeneration in humans.

Patients with a meniscal tear and minimal radiographic signs of OA have been shown in long-term clinical studies to represent a pre-OA population (29). Meniscal injury and meniscal surgery are established risk factors for OA of the knee (29,30). Meniscal tears can be classified as traumatic or degenerative, based on the pattern of the tear. Longitudinal and vertical tears involving the periphery of the meniscus are considered traumatic. Tearing of the meniscus substance generates complex, horizontal, and flap tear patterns that are described as degenerative, and it has been postulated that this type of meniscal tear may be a presenting sign of early OA (29).

Data from this multimodal clinical imaging study are consistent with previous studies showing strong associations between degenerative meniscal tear and preradiographic OA. Mild chondrosis encompasses arthroscopic grades 1 (softening) and 2 (fissuring of $<50\%$ of the cartilage depth). The mean and median arthroscopic grades of 1.6 and 1.5, respectively, are consistent with early chondrosis and the absence of significant OA in this study group.

In this clinical study of patients with degenerative meniscal tears, the OCT findings are potentially consistent with those of ex vivo studies suggesting that OCT may be more sensitive than conventional arthroscopy in identifying early cartilage degeneration. In all of the patients identified by arthroscopy as having abnormally softened cartilage, the OCT cartilage grades were abnormal. Interestingly, while 7 of the 30 patients showed no arthroscopically detectable signs of cartilage abnormality in the area of study, only 2 of the 30 patients had detectable OCT form birefringence by OCT, a property shown in ex vivo studies to be associated with normal structural and metabolic properties of cartilage (10,16,24). While the concept that patients with degenerative meniscal tears represent a pre-OA population lends support to the notion that the high incidence of OCT cartilage-signal abnormality observed in this study may indicate subtle early cartilage degeneration (29), this question cannot be answered through a single cross-sectional study. Similar to the study of any new assessment technology, longitudinal clinical studies to determine whether areas of OCT abnormality progress to cartilage fissuring and tissue loss, as well as additional ex vivo studies comparing OCT signal abnormalities with structural, biochemical, and metabolic abnormalities, are needed.

Because arthroscopy is the current nondestructive clinical standard, it remains unclear whether the relative absence of OCT birefringence in our study was due to clinical OCT detecting degenerative changes at an earlier stage than arthroscopy or if these findings represent a false positive. Previous studies have shown that cartilage that appears "normal" upon arthroscopic examination and visual inspection can be shown to be abnormal upon biochemical and histologic examinations (17,18). Due to ethical considerations, biopsies of "normal-appearing cartilage" were not obtained in this study, and histologic, biochemical, and metabolic assessments were not performed.

Findings of several ex vivo studies of nonhuman articular cartilage suggest that OCT birefringence patterns may reflect alterations to the collagen microstructure (22,24,31,32). Similar findings were noted in a study using human articular cartilage (10). While further research is needed, another ex vivo human tissue study using the same OCT system as was used in the present study showed the absence of detectable OCT birefringence to be associated with cartilage metabolic changes found in early OA (16), thus providing additional insight into the interpretation of these clinical findings.

The findings of this study provide additional support for the feasibility of using OCT to image articular cartilage clinically during arthroscopic surgery in humans (16). The use of infrared light permits ultra high-resolution imaging far exceeding that of current clinical MRI and comparable to that of low-power histologic assessment. OCT imaging is also rapid, with detailed cross-sectional images obtained in near real-time. The area of cartilage imaged in this study was comparable to the area used for histologic analysis from a 2-mm biopsy, but with depth penetration of $\sim$1–1.5 mm. While the superficial cartilage was well-imaged, the penetration depth of OCT was insufficient to assess the deeper layers of human cartilage or the subchondral bone interface. It should be noted that to image articular cartilage, the OCT probe cannot image through skin and must be placed against, or extremely close to, the cartilage through an incision.

Clinical MRI permits noninvasive macroscopic-resolution imaging of articular cartilage and other joint structures but is considered to be limited in its ability to detect cartilage injury and degeneration prior to breakdown of the articular surface (9). For quantitative evaluation of subsurface degeneration, MRI T2 mapping at 3.0T was used in the current study (33,34). Consistent with previous reports, zonal variations in T2 values were observed in this study (35). As a second and

independent measure of cartilage extracellular structure, superficial MRI T2 mapping was found in this study to discriminate between tissue with intact articular surfaces (arthroscopic grades 0–1) and tissue with surface defects (arthroscopic grades 2–4) and to correlate with the quantitative OCT values. While neither the superficial nor the deep cartilage T2 values from the protocols used correlated with arthroscopic grades in this study population in which half of the subjects had intact articular surfaces, the finding that the T2 values in the superficial cartilage correlated with the quantitative OCT values supports additional studies to improve the sensitivity of MRI for the early detection of cartilage abnormalities with either higher-resolution or improved image contrast techniques.

This clinical study additionally showed that both OCT and MRI T2 mapping provide quantifiable data on cartilage subsurface matrix properties. While both qualitative and quantitative OCT values strongly correlated with the findings of arthroscopic assessment of early cartilage degeneration, the MRI T2 values in the superficial cartilage showed a more modest level of correlation with the quantitative OCT values. This is likely due to the differences in resolution between OCT (micrometer) and MRI (millimeter). In contrast, conventional arthroscopy provides micrometer-resolution surface imaging over a macroscopic area, which potentially improves the correlation with both cross-sectional imaging modalities. The larger surface area facilitates comparison with MRI while the high fidelity facilitates comparison with OCT.

Another contributing factor to weak or absent correlations could be the difficulty in ensuring precise registration in the clinical setting. While the use of embedded fiduciary markers, tracking devices, and scoring of the cartilage would better ensure study of the same cartilage sites, these methods are not readily justifiable for use in patients in whom arthroscopic partial meniscectomy is clinically indicated. Despite the registration challenges, this clinical study still showed several important correlations between the 3 metrics. Our findings highlight the importance and potential benefit of multimodal assessments for the enhancement of the diagnosis and staging of early cartilage degeneration.

Clinical study of the natural history of cartilage injury and degeneration prior to breakdown of the articular surface is critically important to the identification of potentially reversible pathologic changes in cartilage (16). In the present study of OCT, a novel imaging technology, the results were found to strongly correlate with arthroscopic findings when used clinically to study articular cartilage. While conventional arthroscopy, the current nondestructive clinical standard for evaluating articular cartilage, permits high-fidelity surface imaging and subjective tactile probing, it does not provide quantitative data on cartilage subsurface structure. Current MRI and MRI T2 mapping protocols lack the speed and resolution of arthroscopy or OCT, but permit noninvasive macroscopic imaging of cartilage subsurface matrix and other joint structures. While the MRI T2 values in this study did not correlate with arthroscopy, the finding that the T2 values in the superficial cartilage correlated with the OCT numerical features, 2 independent quantitative measures of cartilage subsurface properties, supports the continued evaluation of both modalities for the study of early cartilage degeneration.

This study shows that OCT can potentially be used as a clinical research tool to complement arthroscopy by providing quantifiable, microscopic-resolution cross-sectional information on cartilage subsurface characteristics that may be important to the improved evaluation and staging of early cartilage injury and degeneration in humans. Continued research and development of noninvasive and nondestructive clinical tools for the biochemical and quantitative evaluation of cartilage health are needed. Early diagnosis may provide the basis for development of new treatments that can be used to delay or prevent the onset of OA.

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 published. Dr. Chu 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.

Study conception and design. Chu, Kwoh.

Acquisition of data. Chu, Bruno.

Analysis and interpretation of data. Chu, Williams, Tolliver, Irrgang.

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