Technical Developments

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Change in Knee Cartilage T2 at MR Imaging after Running: A Feasibility Study[1]

All participants provided informed consent to participate in this study, which was approved by the institutional review board of Milton S. Hershey Medical Center. The purpose of the study was to determine the feasibility of cartilage T2 mapping in the evaluation of response of femoral and tibial cartilage to running exercise. Quantitative magnetic resonance (MR) T2 maps of weight-bearing femoral and tibial articular cartilage were obtained in seven young healthy men before and immediately after 30 minutes of running by using a 3.0-T MR imager. There was no statistically significant change in T2 profiles of tibial cartilage. There was a statistically significant decrease in T2 of the superficial 40% of weight-bearing femoral cartilage after exercise. These in vivo observations agree well with published ex vivo results and support the hypothesis that cartilage compression results in greater anisotropy of superficial collagen fibers.

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Healthy cartilage requires compressive loading from physical activity to develop normally and maintain form and function (1). However, excessive loading resulting from high-intensity or long-duration exercise can lead to cartilage damage (2). The complex relationship of biomechanics and articular cartilage has resulted in uncertainty with regard to the role of exercise in the development of osteoarthritis (3). In the future, it is likely that noninvasive imaging techniques, such as magnetic resonance (MR) imaging, will provide information that will allow us to better understand the effect of exercise on human cartilage. Both animal models and human epidemiologic studies indicate that exercise is an important factor in normal cartilage physiology and pathophysiology leading to osteoarthritis. Although animal models are necessary to study biochemical and histologic alterations in cartilage that result from exercise, they are poor models of human joint biomechanics. There would be great benefit in monitoring the effects of exercise on cartilage in the intact human joint with physiologic loading conditions.

Initial MR imaging results in the study of cartilage response to exercise have been encouraging. Thus far, most investigators have used MR imaging to determine change in cartilage volume and thickness while exposed to a compressive load (4–6) and after recovery from exercise (7). Changes in signal intensity characteristics (8,9) and relaxation properties (10,11) of cartilage plugs that reflect perturbation in water content and macromolecular organization of compressed cartilage have also been observed with controlled compression experiments. By using a combination of cartilage T2 and T1 measurements obtained after delayed gadolinium enhancement, Nieminen et al (12) were able to accurately predict biomechanical properties of cartilage. Because the T2 relaxation time of cartilage is influenced by water content (13) and collagen fiber orientation (14), it is sensitive to extrusion of water and deformation of collagen fibers that occur with compression of articular cartilage.

Recently, Liess et al (15) demonstrated the feasibility of using cartilage T2 measurements to monitor changes in water content of patellar cartilage during recovery from deep-knee-bend loading of the patellofemoral joint. Since the goal of

their study was to measure change in bulk cartilage T2, they were unable to identify differences in regional response of cartilage to compressive load. This is an important consideration, since there is evidence that compressibility of cartilage is nonuniform, with greater compression occurring near the articular surface (1,16).

We hypothesized that with use of a spatially resolved determination of T2 (ie, cartilage T2 mapping), it may be possible to study regional differences in the response of cartilage to compression in the intact human joint. Thus, the purpose of our study was to determine the feasibility of cartilage T2 mapping in the evaluation of femoral and tibial cartilage response to running exercise.

Materials and Methods

Volunteer Recruitment

Volunteers were recruited from the community and were screened to exclude subjects with a known contraindication for MR imaging. Inclusion criteria included healthy men aged 18–30 years who were not participating in an ongoing exercise program. Women were not included to prevent the potential confounding influence of sex hormones on cartilage T2 and differences in knee biomechanics between the sexes (17). Exclusion criteria were history of prior trauma, orthopedic surgery, chronic disease requiring medical treatment, and joint pain or stiffness.

After the nature of the procedure was explained, all participants provided informed consent to participate in the study, which was approved by the institutional review board of Milton S. Hershey Medical Center. Prior to participating in the study, volunteers completed a Western Ontario and McMaster Universities, or WOMAC, osteoarthritis questionnaire for the assessment of symptoms. Subjects were classified as asymptomatic if their normalized WOMAC score was less than 10. Subjects with a normalized WOMAC score higher than 10 were excluded from further study. Additional demographic data collected included height, weight, self-assessment of frequency and duration of running exercise per week, and participation in a regularly scheduled exercise program. Subject height and weight were used to calculate body mass index by dividing weight in kilograms by the square of height in meters.

Exercise Protocol

To minimize potential diurnal variation in cartilage T2, all subjects were studied in the morning and were instructed to limit weight-bearing activity prior to MR imaging examination. Quantitative T2 maps of the seven volunteers were obtained at baseline and within 10 minutes after completing exercise. Immediately after completion of the baseline MR imaging examination, volunteers were instructed to jog for 30 minutes at a comfortable pace on an asphalt jogging trail. Although the duration of exercise was constant for all subjects, distance and intensity of exercise were not controlled or recorded.

MR Data Acquisition

Quantitative cartilage T2 maps were obtained by using a Bruker 3.0-T MR spectrometer with a 14-cm transmit-receive birdcage coil. Sagittal T2 maps of the femorotibial joint were calculated from a six-section 11-echo sequence with a repetition time of 1500 msec and echo time values spaced evenly over a range of 9–99 msec, 4-mm section thickness, 2-mm intersection gap, 384×384 matrix, 12.75-cm field of view, and no signal averaging. To coregister the locations of the T2 maps before and after exercise, a home-built leg holder was used to rapidly and reproducibly reposition the subject's knee within the MR imager. This device attaches directly to the patient table and MR gradient and radiofrequency coil insert used for knee cartilage T2 mapping studies. In addition to firmly stabilizing the leg during the examination, the device allows for fine adjustment of translational position on three axes, as well as internal and external rotation of the leg. A former placed behind the knee was used to reproducibly reposition the degree of knee flexion on MR images obtained before and after exercise.

Statistical Analysis

Magnitude images and T2 maps were calculated from 10 spin-echo MR images by means of linear least squares curve fitting on a pixel-by-pixel basis with Cincinnati Children's Hospital Image Processing Software/Interactive Data Language (CCHIPS/IDL; RSI, Boulder, Colo) (18). The first echo was excluded from the fit to reduce error resulting from signal produced by stimulated echoes (19). Fitting of the signal intensity (SI) for the ith, jth pixel as a function of time, t, can be expressed as $SI_{i,j}(t) = SI0_{i,j} \cdot \exp(-t/$ $T2_{i,j})$, where $SI0_{i,j}$ is the pixel intensity at $t = 0$ and $T2_{i,j}$ is the T2 time constant of pixel i,j. A magnitude image was generated from the pixel $SI0_{i,j}$ data, and a T2 map was generated from the $T2_{i,j}$ data.

Analysis of the MR imaging results was performed by one investigator (H.E.S.) with more than 3 years of experience in the evaluation of cartilage T2 maps. Regions of interest that were evaluated included tibial and weight-bearing femoral cartilage. The peripheral margin of the meniscus was used to define the anterior and posterior borders of weight-bearing cartilage on the sagittal MR images. To generate regions of interest, segmentation of articular cartilage was performed on each section of the T2 maps by using an interactive subroutine in the CCHIPS/IDL software (RSI).

For the entire region of interest, the software automatically generated multiple T2 profiles by defining perpendicular tangents to the cartilage-bone interface, terminating at the articular surface. The effect of exercise on thickness of tibial and weight-bearing femoral cartilage was evaluated by comparing the mean and standard deviation of the computer-generated tangents for each region of interest with a two-tailed paired t test. A difference in mean cartilage thickness before and after exercise with a P value of less than .05 was considered a statistically significant change.

For comparison of cartilage T2 between volunteers, each profile was normalized for cartilage thickness such that cartilage at the subchondral surface has a normalized distance of 0.0, and cartilage at the articular surface has a normalized distance of 1.0. The T2 profiles of tibial and weight-bearing femoral cartilage before and after running were pooled and fitted to an appropriate response function for analysis by using Systat Table Curve 2D software, version 5.01 (Systat, Richmond, Calif). The 95% confidence intervals for the response functions were calculated as a function of normalized distance from bone. Regions of response function before and after exercise with no overlap of the 95% confidence interval were considered significantly different with a Bonferroni-corrected P value less than .05.

Results

Subject Demographics

Our study included seven men, aged 23–27 years, with a mean age of 25.0 years. Four subjects had a normal weight,
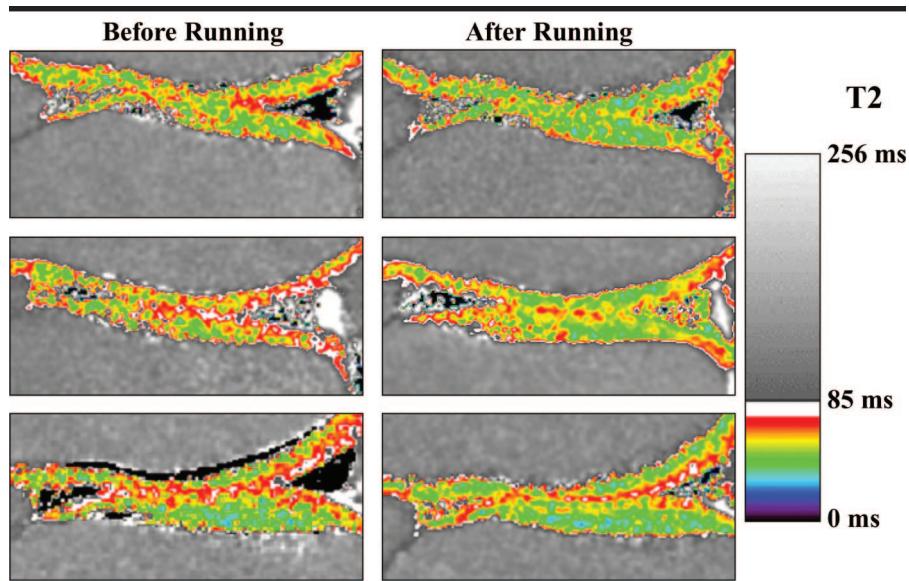
Before Running   **After Running**

Figure 1. Representative sagittal T2 maps of the weight-bearing femorotibial joints acquired in three healthy volunteers before and after 30 minutes of running exercise. T2 maps have been magnified to highlight detail of the weight-bearing femorotibial joint. Spatial variation in cartilage T2 is demonstrated, with longer values occurring near the articular surface. After running, there is loss of superficial red pixels, indicating a decrease in T2 values.

as defined by a body mass index between 18.5 and 24.9, and three subjects were overweight (body mass index between 25.0 and 29.9 kg/m^2), with a mean body mass index of 24.3 kg/m^2. None of the subjects participated in a regular exercise or running program.

Cartilage Thickness

Before exercise, the mean cartilage thicknesses for tibial and weight-bearing femoral cartilage were 2.2 mm ± 0.4 (standard deviation) and 2.3 mm ± 0.5, respectively. After running, a decrease in thickness was observed in six of seven subjects for tibial cartilage (mean decrease, −0.3 ± 0.3; P = .03) and in five of seven subjects for weight-bearing femoral cartilage (mean decrease, −0.2 ± 0.3; P = .29).

Cartilage T2

Representative cartilage T2 maps obtained in three subjects before and after running are presented in Figure 1. All T2 maps demonstrated spatial variation in cartilage T2, with longer values observed near the articular surface. A decrease in superficial cartilage T2 of the weight-bearing femorotibial joint was identified subjectively on the postexercise cartilage T2 maps by a loss of red color-coded pixels at the articular surface. This was confirmed in a quantitative analysis of the cartilage T2 profiles presented in Figure 2.

As seen in Figure 2a, there was no difference in mean cartilage T2 profiles in tibial cartilage after running; however, there was a significant decrease in T2 of the superficial 40% of weight-bearing femoral cartilage after exercise (Fig 2b).

▌ Discussion

High-impact exercise, such as running, subjects articular cartilage to a cyclic compressive load. It is well known that the response of cartilage to compressive load is not uniform (1). Therefore, the ability to spatially localize the response of cartilage to exercise is necessary to study in vivo cartilage biomechanics and function. Results from the present study demonstrate for the first time, to our knowledge, that running results in a statistically significant shortening of superficial cartilage T2 in the weight-bearing femoral condyle.

Because MR imaging allows visualization of the soft tissues of the joint, including cartilage, it can provide information on the response of normal and diseased tissue to biomechanical stress. By using standard clinical MR imaging techniques, small joint effusions (20), increased meniscal signal intensity (20,21), and bone marrow edema (21–23) have been observed after running exercise. Additional studies with high-resolution acquisitions have involved measurement of

change in cartilage deformation in cartilage specimens (10) and cadaveric joints (6,24) with controlled compression conditions.

Few studies have involved the evaluation of cartilage response to exercise in the intact human joint. By using a high-resolution fat-suppressed three-dimensional T1-weighted spoiled gradient-echo MR technique, Waterton et al (25) demonstrated diurnal variation in cartilage thickness of the patellofemoral and weight-bearing femorotibial compartments. In the femorotibial joint, maximal decrease in thickness was 0.65 mm in the lateral compartment and 0.59 mm medially. Eckstein et al (26) demonstrated a 5%–6% decrease in patellar cartilage volume after compressive loading induced by performing 50 deep knee bends. Although our methods for image acquisition were not optimized for measuring change in cartilage morphology, we observed a decrease in cartilage thickness of the weight-bearing femorotibial joint after running that was consistent with tissue consolidation. In our study, weight-bearing femoral cartilage thickness decreased by 7%, while tibial cartilage thickness decreased by 14%.

There have been few investigations on the use of MR parametric mapping techniques to study the response of articular cartilage to exercise. Static compression is known to alter the appearance of articular cartilage on T2-weighted MR images. In an early study on the evaluation of compression on the laminar appearance of cartilage plugs on T2-weighted MR images, Lehner and co-workers (27) observed a pressure-dependent shift in signal intensity that they attributed to an efflux of water from the superficial zone under low pressure that extended to deeper layers with greater compressive load.

Rubenstein et al (8) demonstrated a similar finding in a study of graded compression on cartilage plugs. With low levels of compression, decreased signal intensity developed in superficial cartilage and gradually progressed to deeper layers with greater compression. They hypothesized that the change in signal intensity reflected a combination of net water loss and alteration in collagen orientational structure. These results in excised cartilage samples suggest qualitatively that the response of cartilage T2-weighted signal intensity is nonuniform, with initial changes occurring near the articular surface. Investigators in two studies (15,28) evaluated the effect of exercise on quantitative cartilage T2 measurements in the intact joint.
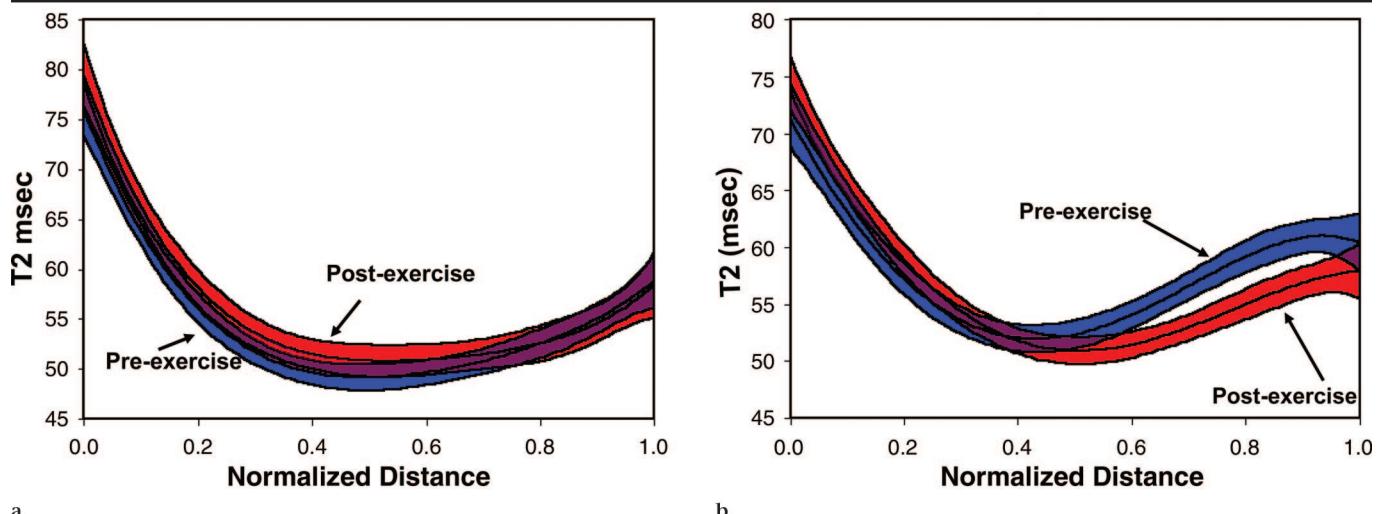
Figure 2. Curves show response of cartilage T2 profiles to running exercise. Mean cartilage T2 and 95% confidence interval of the mean are presented as a function of normalized distance from bone for **(a)** tibial and **(b)** weight-bearing femoral cartilage. The T2 profile for data obtained before running is shown in blue and after running in red; areas of overlap of the 95% CI are in purple. There is no difference in mean tibial cartilage T2 profiles after running. There is a decrease in mean T2 of the superficial 40% of weight-bearing femoral cartilage.

Liess et al (15) demonstrated a 2.6% increase in patellar cartilage T2 over 45 minutes of recovery from deep knee bends, which they attributed to changes in water content. They reported only bulk T2 values and therefore could not determine whether spatial differences in the response of cartilage T2 to compressive load observed with cartilage plugs could be observed in vivo. Recently, differences in T2 between central and peripheral regions of femorotibial cartilage have been observed in response to static in situ compression (28).

Our results demonstrate that in response to physiologic cyclic loading from running exercise, the response of cartilage is nonuniform, with a decrease in T2 occurring in the superficial 40% of femoral cartilage. This observation agrees well with the findings of Lehner et al (27) and Rubenstein et al (8). Biomechanical studies have shown that compressibility of cartilage varies with the distance from the articular surface (1).

Studies involving the use of confocal microscopy and chondrocytes as fiducial markers demonstrate greater compressibility of superficial cartilage compared with deep cartilage of the radial zone (16,29). With joint loading, there is a substantial gradient of compressive strain in cartilage, with large strains of more than 50% near the articular surface, decreasing to 10%–20% in the transitional zone and 0%–5% in the deep and middle radial zones (1). As a result, with physiologic loading conditions, net fluid flux is

limited to the superficial zone of cartilage (1).

It is unlikely that tissue consolidation and the resulting decrease in water content due to efflux of water is the primary factor responsible for the observed change in cartilage T2. Although the percentage thinning of tibial cartilage was nearly twice that of femoral cartilage, we could not demonstrate a statistically significant change in T2 of tibial cartilage. Had the change in T2 resulted from efflux of water in the compressed cartilage, T2 shortening in both femoral and tibial cartilage would be anticipated.

Prior ex vivo studies designed for the evaluation of changes in collagen fiber orientation with loaded conditions suggest that change in fiber orientation is the dominant factor for T2 shortening (11,30). In correlation with polarized light microscopy of porcine femorotibial condyles with static load, Grunder et al (11) attributed the superficial decrease in T2-weighted signal intensity to a pressure-induced increase in thickness of the zone of tangential fibers of the surface layer. Similar findings were reported by Shinar et al (30) by using deuterium double-quantum-filtered spectroscopic imaging. Our in vivo observations are consistent with ex vivo results and support the hypothesis that the decrease in superficial cartilage T2 after running primarily reflects an increase in superficial collagen fiber anisotropy.

Several factors are likely to produce random error in our results and may con-

tribute to the lack of a statistical difference in cartilage T2 changes in tibial cartilage or deeper layers of femoral cartilage. First, since this was a feasibility study, the number of subjects evaluated was small. It is possible that with additional subjects, changes in T2 of tibial cartilage could be identified. Second, we did not measure the degree of compressive load applied to the knee. It is likely that variation in the intensity of running would contribute to individual differences in cartilage loading. Additional studies are needed to determine how different forms of exercise influence cartilage T2 response. Third, variability in positioning of the knee for T2 mapping before and after exercise will lead to random variation in the measured T2 results.

We have shown previously (31) that the pooled coefficient of variation of femorotibial cartilage T2 measurements ranges from 10% to 20% across the femorotibial cartilage T2 profile, with greater variation observed near the cartilage boundaries due to the contribution of volume averaging. However, similar variability in T2 measurements is observed for femoral and tibial cartilage, making it unlikely that this source of random error would lead to a bias in the detection of femoral T2 change but not that of tibial cartilage. Fourth, repositioning of the patient and acquisition of the data set after running resulted in a 10-minute delay. During this period, the knee joint was unloaded, allowing compressed cartilage to recover.

Prior studies indicate that femoral cartilage is stiffer than tibial cartilage (32) and that these sites respond differently to compressive loading. Grunder et al (11) demonstrated in juvenile porcine cartilage plugs that recovery of T2 signal intensity from tibial cartilage after static compression is much faster than that in femoral cartilage. It is likely that the more compressible tibial cartilage recovers to a greater extent prior to obtaining T2 maps after exercise.

In conclusion, these results demonstrate the feasibility of using in vivo MR cartilage T2 mapping to study regional tissue response to physiologic joint loading in the human knee. Our results agree well with prior ex vivo studies on the evaluation of change in T2 signal intensity with static load (11,31,33) and suggest that a change in superficial collagen fiber orientation is likely the mechanism for the observed T2 shortening.

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