Original Research

Effect of Gender on In Vivo Cartilage Magnetic Resonance Imaging T2 Mapping

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Purpose: To determine if gender is a significant variable for in vivo magnetic resonance imaging (MRI) T2-mapping of knee articular cartilage in young asymptomatic volunteers.

Materials and Methods: Cartilage MRI T2 mapping was performed in a young healthy population consisting of seven male and 10 female volunteers, 22 to 29 years of age. High-resolution in vivo T2 maps were obtained of patellar, tibial, and weight-bearing femoral articular cartilage. Spatial dependency of cartilage T2 between groups was evaluated through a comparison of cartilage T2 as a function of normalized distance from bone.

Results: Bulk cartilage T2 values were similar at all three anatomic sites, and between male and female volunteers. All volunteers demonstrated similar spatial variation in cartilage MRI T2 values, with a minimum located in the radial zone and increasing T2 values toward the articular surface. There was no difference in spatial dependency of cartilage T2 between males and females.

Conclusion: In young, healthy volunteers, the magnitude and spatial dependency of cartilage T2 does not differ with gender.

Key Words: cartilage; gender; magnetic resonance imaging; MRI T2; knee
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BECAUSE IT IS NONINVASIVE and can directly image articular cartilage, magnetic resonance imaging (MRI) has recently been considered for clinical assessment of osteoarthritis (OA) (1). While standard anatomic MRI techniques are used to identify morphologic changes in damaged cartilage, such as cartilage volume, thickness, or focal surface lesions, several investigational techniques have been proposed that are sensitive to biochemical and structural changes in the extracellular cartilage matrix (2). The technique of spatially mapping the MRI transverse relaxation time constant (T2) of cartilage has been developed for human application, and has been used in cross-sectional population studies (3–5). Previous studies with cartilage explants have demonstrated that elevated cartilage T2 is correlated with increased cartilage water content (6), loss of type II collagen (7), and loss of collagen fiber anisotropy (8). Because these changes in the extracellular matrix occur very early in OA, and precede morphologic changes such as fibrillation or loss of cartilage, a quantitative measurement of cartilage T2 would potentially provide a sensitive, noninvasive biomarker that could be used to study cartilage physiology and early cartilage damage. However, prior to applying this technique to diseased populations it is necessary to carefully define cartilage T2-mapping in a young healthy population and determine what variables significantly affect this measurement.

Although there are known gender differences in cartilage metabolism (9) and biomechanics (10) of the knee joint that may influence the relaxation properties of articular cartilage, thus far, there have been no studies evaluating the effect of gender on T2-mapping of articular cartilage. Epidemiological studies report a greater prevalence of OA in women (11), with the incidence of OA in females increasing exponentially after age 50 years (12). As with OA, there is a greater prevalence of rheumatoid arthritis in females (13). Because of a larger quadriceps (Q) angle in women, there are substantial gender differences in patellofemoral biomechanics and incidence of patellar malalignment (14). Because the T2 of cartilage is sensitive to changes in cartilage water content resulting from loading of patellar cartilage (6), these biomechanical differences may lead to gender differences in the results of patellar cartilage T2-mapping. To eliminate gender as a potential confounding vari-

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able, previous reports of in vivo cartilage T2-mapping have primarily excluded female subjects (3,4,15,16).

The purpose of this experiment was to determine if there were gender differences in MRI T2-mapping results of knee cartilage in a young, healthy population. Although gender differences in OA are manifest clinically in the middle aged and elderly, it is difficult to isolate the effect of gender in this population due to the effect of other confounding factors. Thus initially, we have chosen to study the effect of gender in a young adult population, controlling for other covariables that may influence cartilage T2 values such as body habitus, level of activity, and diurnal variation. Both cartilage T2 (4), and the incidence of preclinical cartilage damage (17) are known to increase with age. In the elderly population, these additional variables will likely mask any underlying gender effect, and confound the interpretation of results. These factors are less variable in the younger population, providing a more sensitive and specific model to initially study the effect of gender. This is a necessary first step, prior to exploring the more complicated interaction of age and gender on cartilage T2. Furthermore, although the clinical manifestations of OA typically present in middle age, early cartilage damage precedes clinical symptoms by as much as 20 years. Thus in evaluating techniques targeted at early preclinical stages of cartilage degeneration, it is reasonable and necessary to test these techniques in a younger population.

MATERIALS AND METHODS

Volunteer Recruitment

Volunteers were recruited from the community and screened to exclude volunteers with a known contraindication for MRI. Inclusion criteria included healthy adults between the ages of 18 and 30 years. 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. Immediately before the MRI examination, volunteers completed a Western Ontario and McMaster Universities (WOMAC) OA questionnaire to assess symptoms. Volunteers were classified as asymptomatic if their normalized WOMAC score was less than 10. Subjects with a normalized WOMAC score greater than 10 were excluded from further study. Additional demographic data collected included height, weight, and self-assessment of level of exercise. All studies were conducted in the morning to minimize the potential effect of diurnal variation. Female volunteers were studied between day 7 and day 14 of their menstrual cycle. Male and female cohorts were matched for age, body mass index (BMI), and activity level.

MRI Data Acquisition

Patients were scanned supine in the magnet such that the patellar articular surface was parallel to B0. The weight-bearing femoral and tibial cartilage articular surface was perpendicular to B0. Knees of 10 asymptomatic females (ages 22–29 years) and seven males (ages 22–29 years) were evaluated with a Bruker 3.0 T MR imaging-spectrometer using a 14-cm transmit-receive birdcage coil. Sagittal proton density and T2 maps of the femoral tibial joint were calculated from a six-section, 11-echo sequence with TR/TE = 1500/10–100 msec, 4-mm section thickness (ST), 384 × 384 image matrix, 12.75-cm field of view (FOV), and no signal averaging. Axial T2 maps of the patellofemoral joint were obtained from five sections with a 3-mm ST, 256 × 256 image matrix, and a 14.00-cm FOV. Image acquisition times for the sagittal and axial T2 mapping studies were 9.6 minutes and 6.4 minutes, respectively.

Data Analysis

Magnitude images and T2 Maps were calculated from 10 spin-echo images by means of linear least squares curve fitting, on a pixel-by-pixel basis with CCHIPS/IDL software (Cincinnati Children's Hospital Image Processing Software/Interactive Data Language, RSI, Boulder, CO) (4). Fitting of the signal intensity (SI) for the ith,jth pixel as a function of time, t, can be expressed as follows:

$$SI_{i,j}(t) = SI0_{i,j} \cdot \exp(-t/T2_{i,j}),$$

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 is generated from the pixel $SI0_{i,j}$ data, and a T2 map is generated from the $T2_{i,j}$ data.

Regions of interest (ROIs) that were evaluated included patellar, tibial, and weight-bearing femoral cartilage. The peripheral margin of the meniscus was used to define the anterior and posterior border of weight-bearing cartilage on the sagittal images. To generate ROIs, segmentation of articular cartilage was performed on each section of the T2 maps using an interactive subroutine in the CCHIPS/IDL software. For the entire ROI, the software automatically generates multiple T2 profiles by defining perpendicular tangents to the cartilage/bone interface, terminating at the articular surface. For comparison 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.

For each cohort, T2 profiles of patellar, tibial, and weight-bearing femoral cartilage were pooled and fit to an appropriate response function for analysis. The 99.99% confidence intervals (CI) for the response functions were calculated to determine differences in T2 between groups as a function of normalized distance from bone. Regions of the response function with no overlap of the 99.99% CI were considered significantly different with a Bonferroni-corrected P value < 0.05.

RESULTS

None of the subjects recruited participated in a regular exercise program or organized athletic activity. The average BMI for the female cohort was 22.9 (range: 21.5 to

Table 1
Bulk Cartilage T2 (Mean ± SD)

Site	Male T2 (msec) $N = 7$	Female T2 (msec) $N = 10$
Patella	55.1 (8.8)	53.8 (8.7)
Tibia	55.1 (7.2)	56.3 (6.9)
Femur	57.9 (5.2)	57.0 (5.3)

24.0), and for the male cohort it was: 23.0 (range: 21.5 to 24.4).

As summarized in Table 1, there was no statistically significant difference in bulk cartilage MRI-T2 values for male and female volunteers. For both male and female subjects the longest mean T2 values were obtained from the weight-bearing femoral cartilage, however, bulk cartilage T2 values did not differ significantly between sites.

Figure 1 demonstrates representative axial cartilage T2 maps of female and male volunteers. All volunteers demonstrated spatial variation in articular cartilage T2, with minimum values occurring in the radial zone of cartilage and increasing toward the articular surface.

The spatial variation in T2 with distance from bone is better appreciated as cartilage T2 profiles, as presented in Fig. 2. For both male and female volunteers, the greatest spatial variation in T2 was observed in patellar cartilage. For male volunteers, the minimum T2 value in patellar cartilage of 45.9 ± 3.3 msec (mean ± 99.99% CI) occurred at a normalized distance of 0.3 from the bone, with cartilage T2 increasing to 67.4 ± 7.2 msec at the articular surface. For female patellar cartilage, the minimum T2 value of 44.9 ± 1.9 msec occurred at a normalized distance of 0.4, with T2 increasing to 67.4 ± 4.2 msec at the articular surface. For both male and female subjects, less spatial variation in cartilage T2 was observed in femoral and tibial cartilage. The shaded intervals of the cartilage T2 profiles in Fig. 2 represent the 99.99% confidence interval of the population mean as a function of normalized distance from the bone. For the patellar, tibial, and weight-bearing femoral cartilage, the T2 profiles overlap over the entire distance, indicating no statistical difference in cartilage T2 profiles between male and female cohorts.

DISCUSSION

Prior studies have demonstrated sensitivity of cartilage T2 to changes in water content (6), collagen content (7), and collagen fiber orientation (18,19) in the extracellular matrix. Because of the high sensitivity of T2 to factors that alter the biochemical and structural organization of cartilage, it is necessary to identify variables that may influence results of in vivo cartilage T2-mapping prior to extending this techniques to large, expensive, population studies.

Epidemiologic studies have identified female gender as a statistically significant risk factor in development of both OA and rheumatoid arthritis, independent of weight and physical activity (17). In reference to OA and gender, men have a higher incidence of OA between the ages of 20 years to approximately 50 years; beyond this age, however, women show a marked increase in the incidence of OA, suggesting an effect of estrogen (20). Gender also influences the pattern and distribution of OA, with certain sites such as the hand (21) demonstrating a female predilection. In addition, other musculoskeletal disorders such as chronic patellofemoral pain syndrome are more common in female patients (10). Gender differences in knee OA have been attributed both to differences in joint biomechanics and to hormonal effects on cartilage.

Epidemiologic evidence of a hormonal effect of estrogen on cartilage is not clear, with studies demonstrating both a beneficial and deleterious effect of hormone replacement therapy on the risk of developing OA (22,23). Biochemical evidence supports a role of sex hormones in cartilage metabolism that may influence the pathogenesis of OA. Estrogen receptors have been identified in articular cartilage, and estrogen replacement therapy in surgically menopausal monkeys results in increased proteoglycan synthesis by chondrocytes (24). Prior studies in rats have demonstrated gender differences in biochemical composition of the

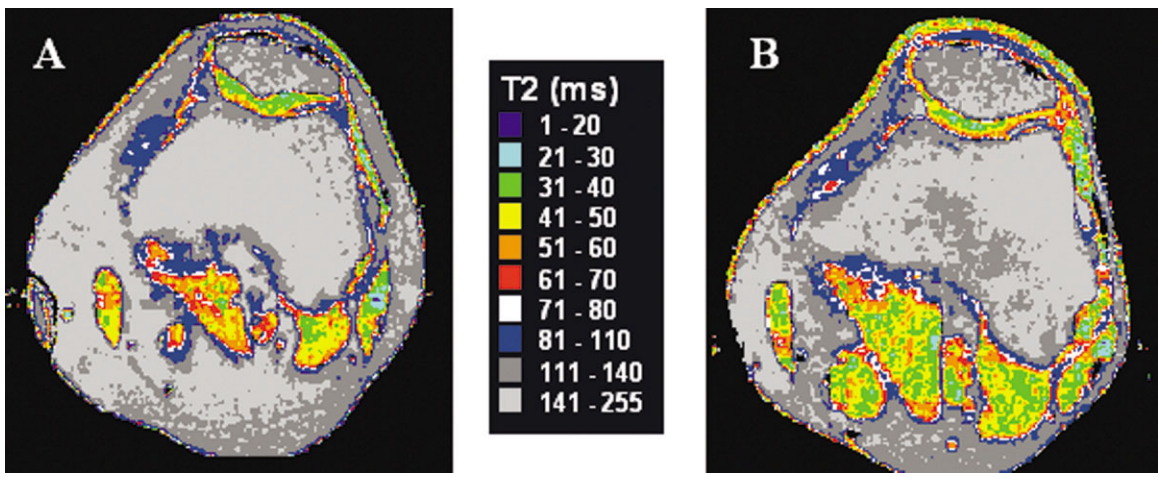

Figure 1. Representative axial MRI T2 maps of asymptomatic female (**A**) and male (**B**) volunteer. Both T2 maps demonstrate a similar pattern of T2 variation in patellar cartilage with longer T2 times near the articular surface.

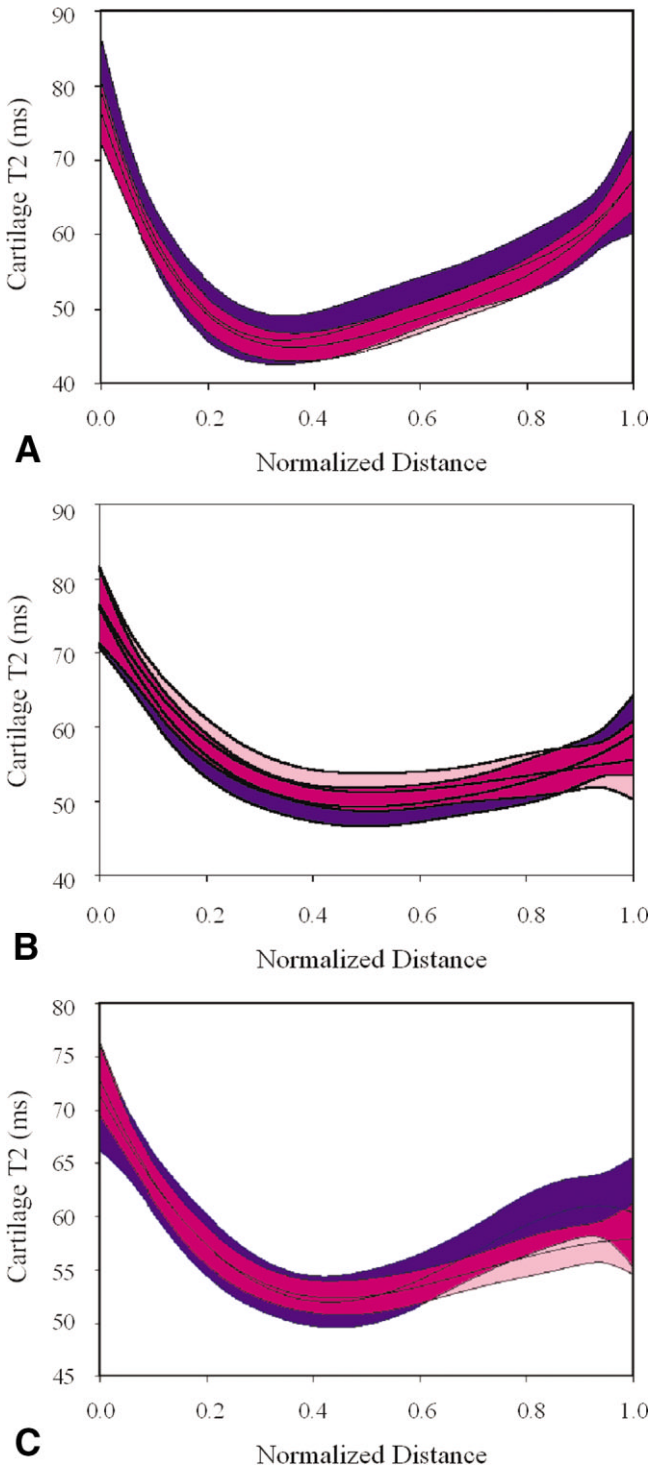

Figure 2. Pooled normalized cartilage T2 profiles for (**A**) patellar, (**B**) tibial, and (**C**) weight-bearing femoral cartilage. Shaded regions represent the 99.99% confidence interval of the mean for the male (blue) and female (pink) cohorts. Regions of overlap are shown as dark pink. All sites demonstrate a similar spatial variation in cartilage T2 as a function of distance from bone. There is no statistically significant difference in T2 spatial variation for the male and female populations.

extracellular cartilage matrix and the propensity for cartilage degradation, with male Wistar rats having a greater concentration of both proteoglycan and collagen (9). In a recent study measuring urinary degradation products of cartilage type II collagen, Mouritzen et al (25) demonstrated statistically significant differences in type II collagen turnover as a function of body habitus, age, menopausal status, and gender. In this study, gender differences were minimal before age 45 years, but increased suddenly with the onset of menopause, suggesting a strong hormonal effect on cartilage collagen metabolism. Additional studies are needed to determine if a similar perimenopausal hormonal effect is observed in cartilage MRI T2-mapping, which has been demonstrated to be sensitive to the degradation (7) and orientation (18) of the type II collagen matrix.

Thus far, studies evaluating the effect of gender on MRI evaluation of articular cartilage have focused on differences in cartilage volume and thickness. Two recent MRI studies using T1-weighted gradient echo imaging demonstrated statistically significant smaller knee cartilage volumes in females compared to males, independent of differences in body mass (26,27). This is primarily a result of a larger articular surface area in males, as there was no significant difference in cartilage thickness. A more recent study evaluating the effect of age and gender on MRI evaluation of cartilage thickness found reduced femoral cartilage thickness in both sexes, and reduced patellar cartilage thickness in elderly women (28). Several studies have looked specifically at sex hormones and cartilage volume. A recent MRI study identified 10% greater knee cartilage volume in women using long-term estrogen replacement therapy compared to age-matched postmenopausal females, suggesting a potential hormonal effect on preservation of articular cartilage (29). No protective effects of estrogen replacement therapy were identified for patellar cartilage (30). Cicuttini et al (31) have hypothesized that testosterone may be a factor in explaining gender differences in tibial cartilage volume and prevalence of femoral/tibial OA. Thus far, studies evaluating the effect of gender on the MRI of cartilage have been limited to morphologic studies. Although there is evidence to indicate estrogen influences biochemical composition of the extracellular cartilage matrix, no studies have been conducted to determine if MRI parametric mapping techniques, which are potentially sensitive to these changes, are influenced by gender.

Our results demonstrate a similar magnitude and spatial dependency of articular cartilage T2 for young, healthy, male and female volunteers, indicating gender is not a significant covariable in this age group. As described in prior cartilage T2-mapping studies of human cartilage, all volunteers demonstrated spatial dependency of cartilage T2 with distance from bone. The initial study by Dardzinski et al (3) found a minimum T2 value of 34 msec in the radial zone, increasing to 57 msec at the articular surface. Using slightly different methods of segmentation and data analysis, a similar spatial distribution in male patellar cartilage T2 was observed by Mosher et al (4). This study demonstrated an age dependency of cartilage T2 with higher values

observed in superficial cartilage for male volunteers over age 45 years. Our results, which demonstrated the greatest spatial dependency of T2 in patellar cartilage and less spatial variation in femoral and tibial cartilage, agree well with findings previously reported by Smith et al (5).

Error resulting from the effects of stimulated echo signal and magnetization transfer limit the accuracy of quantitative T2 measurements obtained with a multisection multiecho acquisition (32). Additional error may result at cartilage boundaries due to volume averaging, chemical shift artifact (5), and short T2 values observed near the bone/cartilage interface (33). Because identical data acquisition and analysis methods were used for both cohorts, these errors should affect both equally, and thus are unlikely to introduce a systematic bias.

The results of this study should not be extrapolated to other MRI parametric mapping techniques used in evaluation of cartilage. MRI T2 values are primarily influenced by collagen concentration and fiber orientation (7), as well as water content (6), and are relatively insensitive to change in proteoglycan content (34). If estrogen therapy increases proteoglycan synthesis in humans, this may result in a gender difference detectable with MRI techniques reported to be sensitive to proteoglycan concentration, such as delayed gadolinium enhanced MRI of cartilage (dGEMRIC) (35), T1ρ MR imaging (36), or ^{23}Na MRI (37).

In conclusion, the spatial variation in cartilage T2 of the knee of premenopausal, young asymptomatic females is consistent with that previously reported for similar male cohorts when matched for age, activity, and body habitus. In this population, gender does not significantly alter the magnitude or spatial dependency of cartilage T2. Additional studies are needed to compare postmenopausal females, and to evaluate the effect of age in the female population.

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