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The Natural Degeneration Course in the T1rho Values of Normal Knee Cartilage

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The purpose of our study is to investigate whether there is an age-related change in T1 rho values and to evaluate the effects of weight bearing on age-related increase in T1 rho values of normal cartilage. Thirty-two asymptomatic patients were examined using a 3.0T MRI to determine knee cartilage T1 rho values. Femorotibial and patella cartilage was defined as weight-bearing cartilage (WB-C) and non-weight-bearing cartilage (NWB-C), respectively. The femoral cartilage was divided into weight-bearing (WB-P) and less-weight-bearing (LWB-P) portions. Pearson's correlation coefficient and single regression analysis were used to assess the relationship between cartilage T1 rho values and age. The slopes of the regression lines of cartilage T1 rho values and age were compared between WB-C and NWB-C and between WB-P and LWB-P. Cartilage T1 rho values correlated positively with aging for all cartilage regions and all age groups ($p < 0.001$). In the medial femoral cartilage, the age-related increase in T1 rho values was significantly greater for WB-P than for NWB-P ($p < 0.05$). For several cartilage regions, this increase was greater for WB-C than for LWB-C ($p < 0.05$). The T1 rho value is very sensitive to age-related cartilage degeneration and weight bearing-related degeneration, and hence may be a very sensitive and useful measure for the early diagnosis of osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is associated with degeneration of articular cartilage and a common cause of disability especially in persons over the age of 50 years with a significant negative impact on the quality of life of elderly individuals [1]. Because the incidence of OA continues to increase with the aging population, there is a great need noninvasive assessment of cartilage damage for the evaluation and validation of disease modifying osteoarthritis drugs. The current diagnostic gold standard for diagnosing osteoarthritis is the assessment of joint space narrowing on weight bearing radiography. However, these measurements frequently underestimate cartilage damage and vary with the degree of knee flexion.

Magnetic resonance imaging (MRI) has improved greatly during the past decade and allows for precise noninvasive visualization of joint structures. Conventional MRI techniques (including fat saturated T2-weighted, proton density-weighted fast spin echo (FSE) and T1-weighted spoiled gradient echo (SPGR) sequences) are useful tools for assessing cartilage morphology. It has been suggested that prior to morphologic cartilage change, early

degenerative change in cartilage are associated with biochemical changes such as loss of proteoglycans, changes in water content and minor structural changes in collagens [2, 3]. Although conventional standard MRI techniques provide excellent detection of late-stage degenerative cartilage changes, these techniques are not sufficiently sensitive to detect and quantify the early change of osteoarthritis including disruption or alteration of the cartilage matrix [4].

Recent developments of novel surgical approaches, such as chondroprotective therapies, cartilage grafting, and gene therapy, require accurate and noninvasive techniques for detecting *in vivo* changes that are characteristic of the initial stages of cartilage degeneration and for postoperative monitoring of cartilage. Hence, biochemical MRI techniques at 3.0T have been established to quantify cartilage matrix composition regarding proteoglycan concentration and collagen integrity. These new MRI techniques are sufficiently sensitive for the detection of structural and functional cartilage changes during the early stages of OA, and could be valuable techniques for identifying the need for early treatment, monitoring response to treatment and assessing efforts to prevent disease progression [3, 5].

Spin-lattice relaxation in the rotating-frame T1 ρ is a novel MRI technique that is sensitive and specific to the slow macromolecular interactions especially in the low-frequency range (0-100kHz) in contrast to conventional spin-lattice relaxation time (T1). These slow macromolecular motions are generally characterized by correlation time (τ_c), and T1 ρ is most sensitive to processes when condition $\omega_1 = 1/\tau_c$ is fulfilled. T1 ρ describes the spin-lattice relaxation in the rotating frame, and changes in the extracellular matrix of cartilage, especially the loss of proteoglycan, may be reflected in measurements of T1 ρ because of less restricted motion of water protons. Recent studies have shown that cartilage T1 ρ values are longer in cartilage of early OA patients [6-8]. Several recent *in vivo* studies investigating T1 ρ values in human OA revealed significant differences in T1 ρ value between patients with early stage OA and normal controls [9-17]. While the T1 ρ value has recently been proposed as an attractive alternative parameter for diagnosing early OA, experimental researchers ask for caution in using this marker. Not only T1 ρ but also other novel biochemical MRI parameters are highly sensitive to many competing factors in cartilage and might lead to misinterpretation of progression or regression of OA [18]. While both weight bearing and aging are important factors in normal and pathological cartilage physiology leading to OA [19], only few studies have assessed age-related [10,14,19,20] or weight bearing-related [11,12,16] degeneration of knee cartilage using T1 ρ *in vivo* and *in vitro*. Knowledge of normal age-related changes of cartilage T1 ρ values is a prerequisite for identifying an association of T1 ρ values with early asymptomatic damage. In addition, understanding the relationship between weight bearing and T1 ρ values in normal cartilage would be of great benefit for accurate diagnosis and monitoring early OA even before morphologic change emerge.

The goal of this study was to investigate whether there is an age-related change in T1 ρ values of normal cartilage and to evaluate the effects of weight bearing on T1 ρ values in normal cartilage. We hypothesized that (a) T1 ρ values are positively correlated with age in various regions of the knee and that (b) the age-related increase in T1 ρ values is greater in weight-bearing regions.

MATERIAL AND METHODS

Subjects

Thirty-two asymptomatic patients (32 women, mean age $\pm$ SD, 41.6 $\pm$ 13.4 years) were examined using a 3.0T MRI for T1 rho mapping. Inclusion criteria for all subjects were good health according to their medical history, physical examination and clinical laboratory data, and absence of contraindication for MR imaging. Only subjects with intact joint function with full strength, no history of chronic or frequent knee pain, and normal body mass index (BMI) were included in this study. After the nature of the procedure was explained, all participants provided informed consent to participate in the study, which was approved by the Committee on Human Research of our institution. The right knee of each patient was scanned for both T1 rho values and T2 mapping.

Imaging protocol

All MR exams were implemented on a 3T Philips Achieva QD R.3.1.1.2. (Koninklijke Philips Electronics N.V., Eindhoven Netherlands) using a quadrature transmit/receive knee coil. The protocol included six sequences: sagittal T1-weighted spin echo (SE) imaging (TR/TE=600/10ms, FOV=15cm, matrix=512 $\times$ 512, bandwidth=230Hz/pixel, number of excitations[NEX]=1), sagittal fat-saturated T2-weighted fast spin echo (FSE) images (3mm/1mm 20slice, TR/TE=3000/60ms, FOV=15cm, matrix=512 $\times$ 512, slice thickness=3mm, bandwidth=219.1Hz/pixel, echo train length[ETL]=12, NEX=1), and T2-weighted images (3mm/1mm 20slice, TR/TE=3000/60ms, FOV=15cm, matrix=512 $\times$ 512, slice thickness=3mm, bandwidth=219.1Hz/pixel, echo train length[ETL]=12, NEX=1), PDW SPIR images (3mm/1mm 20slice, TR/TE=4000/20ms, FOV=15cm, matrix=512 $\times$ 512, slice thickness=3mm, bandwidth=289.7Hz/pixel, echo train length[ETL]=12, NEX=1), and T1 rho-weighted.

T1 rho mapping

Sagittal T1 rho-weighted images were obtained using the spin-lock technique and spiral image acquisition. The following acquisition parameters were used: 3D-balanced-TFE, 20interleaves/slice, 4096 points/interleaf, FOV=15cm, matrix=256 $\times$ 256, effective inplane spatial resolution=0.3 $\times$ 0.3mm, slice thickness4mm, number of slices=20, TR/TE=4.8/2.4ms, time of spin-lock (TSL)=01/10/20/30/40ms, FA=50°, Fat.Sat=SPIR and spin-lock frequency=759.5Hz/pixel. The total acquisition time was 12min 42s. The T2 quantification sequence was with TR/TE of 2792/11,100ms. All other prescription parameters of the T2 sequence were the same as those for the T1 rho sequence with a total acquisition time of 8min 50s. MRI scans were performed in one continuous session without removing the subject from the scanner. Measurements were conducted in the evening between 5–7 p.m. T1 rho maps of hyaline cartilage was reconstructed by fitting the T1 rho weighted image intensity pixel-by-pixel to the equation below using an in-house Levenberg-Marquardt mono-exponential fitting algorithm written in C:

$$S(\text{TSL}) \propto \exp(-\text{TSL}/\text{T1 rho})$$

where TSL is the time of spin lock, S is the signal intensity in a T1 rho weight image with a certain TSL. MR images were transferred to a Dell workstation (Dell Inc, Round Rock, Tex) for off-line quantification of cartilage T1 rho relaxation times. T1 rho-weighted images with the shortest TSL (therefore with highest SNR) were rigidly registered to high-resolution T1-weighted SPGR images acquired in the same exam using the VTR CISC Registration Toolkit. The transformation matrix was applied to the reconstructed T1 rho map.

Fig. 1-a

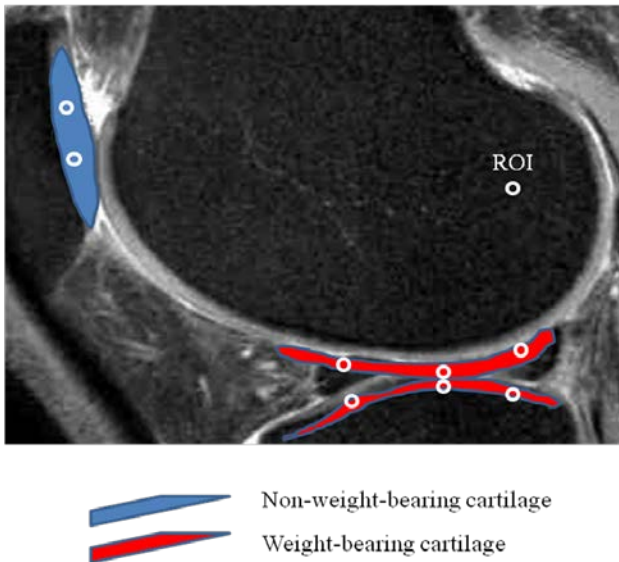


Figure 1a. Illustration of the partitioning of knee cartilage into weight-bearing regions (WB-C) and non weight-bearing regions (NWB-C). Patella cartilage (shown in blue) was defined as non-weight-bearing cartilage (NWB-C) and femorotibial cartilage (shown in red) was defined as weight-bearing cartilages (WB-C).

Fig. 1-b

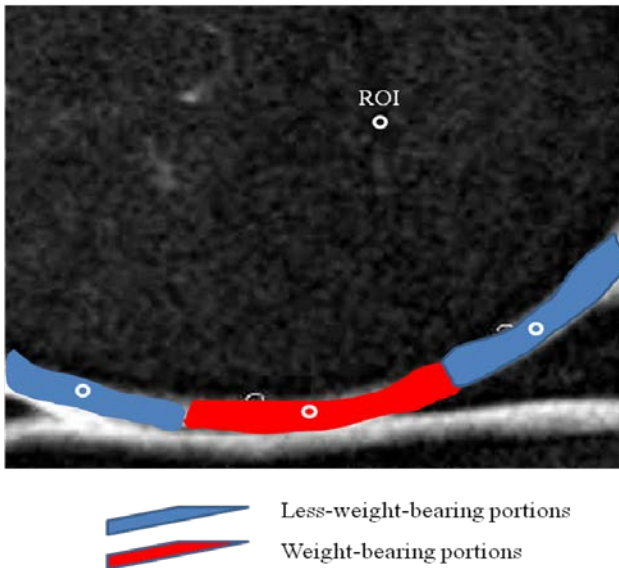


Figure 1b. Illustration of the partitioning of femoral cartilage into weight-bearing regions (WB-P) and less weight-bearing regions (LWB-P). Cartilage adjacent to the anterior or posterior horns (shown in blue) was defined as WB-P and the uncovered portion of femoral cartilage between the free edge of the anterior and posterior meniscus horns (shown in red) was defined as LWB-P.

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MR imaging analysis

All MR images were evaluated by three radiologists. Regions of interests (ROI) were manually drawn by three experienced radiologists (M.F., Y.I., H.G.) in consensus with normal cartilage definition. Normal cartilage was defined as cartilage where thickness was preserved, the surface was intact and no intrachondral signal alteration was visible. The sizes of all ROIs were similar size within each cartilage. The volume of each ROI was standardized to an area of 1mm^2 . Attention was paid at the edges of the ROIs the avoid sampling of joint fluid or subchondral bone.

Patella cartilage was defined as non-weight-bearing cartilage (NWB-C) and femorotibial cartilage was defined as weight-bearing cartilage (WB-C) based on SPGR sagittal images. Four compartments were defined in the femoral-tibia joint: lateral femoral cartilage, medial femoral cartilage, lateral tibia cartilage and medial tibia cartilage. Each lateral femoral cartilage and medial femoral cartilage was partitioned into weight-bearing portions (WB-P) and less weight-bearing portions (LWB-P) (Fig. 1). Cartilage adjacent to the anterior or posterior horns was defined as WB-P and the uncovered portion of femoral cartilage between the free edge of the anterior and posterior meniscus horns was defined as LWB-P. In the lateral and medial femur, three ROIs were manually drawn. Two ROIs were selected in WB-P that were in direct contact with the opposing tibia cartilage, one ROI was selected in anterior LWB-P that was covered by anterior meniscus, and one ROI was selected in posterior LWB-P that was covered by posterior meniscus. In addition, one ROI was selected in each weight-bearing region. In the lateral and medial tibia, three ROIs were selected for each joint. One ROI was selected in the region covered by the anterior meniscus. One ROI was selected in the region between the anterior and posterior menisci. One ROI was selected in the region covered by the posterior meniscus. Average T1 rho values were calculated as the average of value of these three ROIs. In patella cartilage, two ROIs were selected and the average T1 rho value for these two ROIs was computed.

Statistical analysis

Mean and standard deviation (SD) of T1 rho values were calculated for each of cartilage region for all subjects. Pearson's correlation coefficient and simple linear regression analysis were used to assess the relationship between age and T1 rho values in each region. Thus, the slopes of the linear regression lines represented the age-related change in T1 rho values. The slopes of the linear regression lines for NWB-C and WB-C were compared using Dunnett's test. The slope of the linear regression lines for LWB-P and WB-P were compared using two-tailed t-test. P-values <0.05 were considered statistically significant. All statistical analyses were performed using JMP software version 8.0 (SAS Institute Cary NC) and SPSS software version 17.0 (SPSS Chicago USA).

RESULTS

Average T1 rho values for all regions are presented in Table I. Paired t-tests did not detect any significant differences in T1 rho values between most regions. Only T1 rho values for patella regions were significantly higher than those for other regions.

Table I. T1rho value in each cartilage region

	Medial femur		Lateral femur		Medial tibia		Lateral tibia		Patella
	Weight-bearing	Non-weight-bearing	Weight-bearing	Non-weight-bearing	Weight-bearing	Non-weight-bearing	Weight-bearing	Non-weight-bearing	
T1ρ [msec]	53.0 ± 11.4	49.9 ± 11.0	53.3 ± 10.6	51.1 ± 10.6	53.1 ± 12.3	46.0 ± 9.9	51.9 ± 13.4	49.5 ± 12.8	64.3 ± 8.9
95%CI	48.3–57.5	46.1–53.8	48.9–57.8	47.0–55.2	48.5–57.6	41.8–50.2	46.5–57.2	44.6–54.5	60.9–67.8

Note.-Data are mean value ± standard deviations

T1 rho and aging

Table II shows that a significant relationship between age and T1 rho values was detected for each region. The relationships between age and T1 rho values ranged from strong to moderate positive correlations.

Table II. Correlation between the T1rho value and age in each cartilage region

	Medial tibia	Lateral tibia	Medial tibia	Lateral femur	Medial femur	Lateral femur	Medial femur	Lateral femur	Patella
	weight-bearing	weight-bearing	non-weight-bearing	non-weight-bearing	weight-bearing	weight-bearing	non-weight-bearing	non-weight-bearing	
slope	0.5824	0.5579	0.5600	0.6344	0.7017	0.5313	0.4040	0.4170	0.3564
R ²	0.4039	0.3700	0.4878	0.5389	0.6139	0.4947	0.3164	0.4154	0.2863
prob>F	p<0.0001**	p<0.0001**	p<0.0001**	p<0.0001**	p<0.0001**	p<0.0001**	p=0.0018**	p=0.0002**	p=0.0034**

Note.-**significant positive correlation (p < 0.05)

Age, T1 rho and weight bearing

Independent samples t-tests revealed significantly greater slopes of the regression line in WB-P than in LWB-P only for medial femoral cartilage (P<0.05; Fig. 2). Thus, in medial femoral cartilage, T1 rho values increased more with increasing age in WB-P than in NWB-P. Similarly, significantly greater slopes of the regression line were found for WB-C compared with NWB-C for medial femoral and lateral tibia cartilage. Finally, a trend toward greater slopes of the regression line for WB-C compared with NWB-C was found for the medial tibia (p=0.06) and lateral femoral cartilage (p=0.09) (Fig. 3). Thus, in medial tibia and lateral femoral cartilage there was a trend of greater increases of T1 rho values with increasing age in WB-C than in NWB-C.

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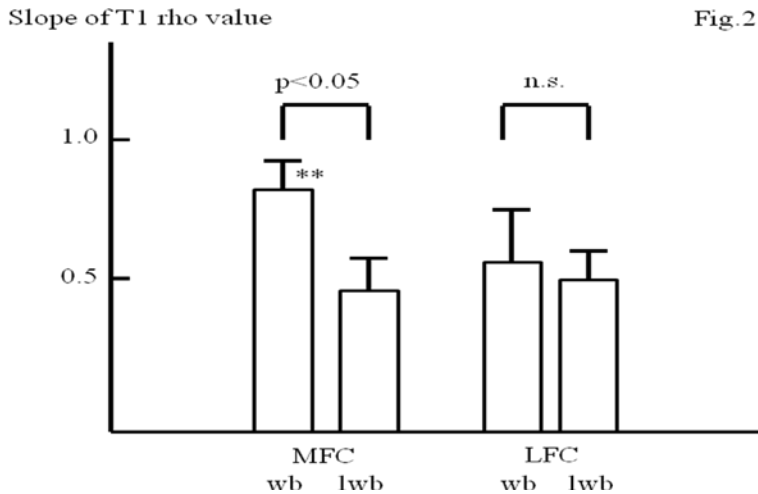


Figure 2. Age-related increase in T1 rho values for LWB-P and WB-P. The age-related increase in T1 rho values in the medial femoral cartilage was significantly greater in WB-P than in LWB-P ($p=0.029$).

MFC=medial femoral cartilage, LFC=lateral femoral cartilage, wb=weight-bearing portion, lwb=less weight-bearing portion.

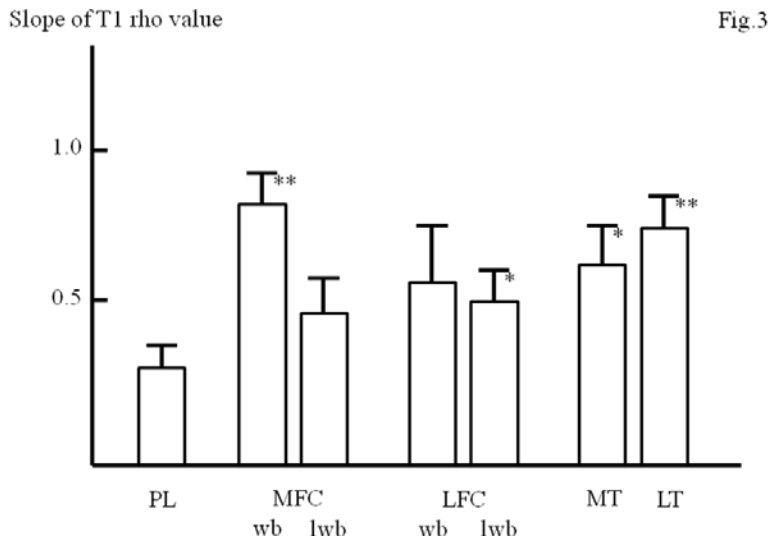


Figure 3. Age-related increase in T1 rho values for NWB-C and WB-C. The age-related increase in T1 rho values was significantly greater in WB-P of the medial femoral and lateral tibial cartilage than in NWB-C of the patella indicated by **. A trend toward greater age-related increase in T1 rho values in medial tibia ($p=0.06$) and lateral femoral without weight bearing ($p=0.09$) compared with the patella is indicated by *. PL=patella cartilage, MFC=medial femoral cartilage, LFC=lateral femoral cartilage, MT=medial tibia cartilage, LT=lateral tibia cartilage, wb=weight-bearing portion, lwb=less-weight-bearing portion.

DISCUSSION

Three newer biochemical MRI techniques (T1 rho value, delayed gadolinium-enhanced proton MRI (dGEMRIC), and sodium MRI) with the potential to reflect molecular level proteoglycans changes have been used to assess the loss of proteoglycan in cartilage degeneration that may occur prior to morphologic cartilage changes in OA [7, 21]. However, limitations of delayed gadolinium-enhanced proton MRI (dGEMRIC) include the need for a sixty to ninety-minute wait after gadolinium injection (either intravenously or intra-articularly) to optimize penetration of the contrast agent. Furthermore, dGEMRIC requires two image sequences (pre-contrast and delayed post-contrast) which increases the total data acquisition time for patients. While sodium MRI is highly specific to proteoglycan, this MRI technique requires radiofrequency hardware modification and high static magnetic fields (B0) and inherently low sensitivity. In contrast, the T1 rho value method is a quantitative method based on the spin-locking technique and reflects the slow motion interactions between motion-restricted water molecules and their local macromolecular environment. One of the advantages of the T1 rho value method is that it does not require the use of a contrast agent. Moreover, the T1 rho value method can be implemented in a clinical environment without hardware modifications. Thus, the T1 rho value method has been proposed as being the most attractive candidate for diagnosing early OA.

Relation between aging and T1 rho values

The results of this study revealed a statistically significant positive linear correlation between age and cartilage T1 rho values for all regions. Elevated T1 rho values represent the loss of proteoglycan from cartilage. Two previous studies evaluated differences in cartilage T1 rho values between age groups in asymptomatic subjects [10, 14]. These articles showed that in normal cartilage, the relationship between age and percent change in total or average T1 rho value is close to linear. Our result confirmed these previous observations. Rauscher *et al.* showed that T1 rho values are substantially affected by age [20]. Based on these result, we speculate that age-related loss of proteoglycan occurs in all age groups and leads to a linear increase in T1 rho values. One of the first events in articular cartilage degeneration is the disruption or alteration of molecular structure and composition of the matrix, and the most striking articular cartilage matrix change with increasing age is alteration in aggregating proteoglycan [21]. Bobacz *et al.* showed that both chondrocyte numbers and synthesis of normal proteoglycan from healthy cartilage decrease with increasing age [22]. Some articles reported that the size of proteoglycan aggregates decreases significantly with increasing age because of shorter chondroitin sulfate chains and irregularity of aggregates [23-26]. Additionally, an age-related increase in the production of insulin-like-growth-factor-I decreases the ability of chondrocytes to maintain or repair the articular cartilage matrix [27] and a higher concentration of glycation end products negatively affect proteoglycan synthesis [28]. According to the telomere erosion hypothesis, telomere length correlates with phenotypic measures of senescence which offers one possible explanation for chondrocyte senescence. Martin and Buckwalter observed that mean telomere length in human articular cartilage declines in all age groups, that there is a significant negative linear correlation between telomere length and age in all age groups (1-87 years), and that senescent chondrocytes accumulate with cartilage age [29]. Our present hypothesis agrees well with these previous results. Recent research found that the presence of oxidative stress induces telomere genomic instability, and telomere genomic instability promotes the senescence and dysfunction of chondrocytes [30].

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While many studies have reported OA related changes to cartilage assessed using biochemical MRI, only few articles investigated age-related changes in normal cartilage using biochemical MRI. Mosher et al. stated that the biochemical MRI parameter T2 reflects the extent and location of degeneration of the collagen matrix, however, an age-related linear increase in knee cartilage T2 values in asymptomatic volunteers was reported only for volunteers over the age of 45 years [31, 32]. Below the age of 45 years, there was no significant correlation between age and T2 value in normal cartilage. This published evidence appears to conflict with our observation of age-related cartilage T1 rho value changes.

The discrepancy between age-related changes of T1 rho values and those of T2 values can be explained by degeneration processes of cartilage contents. The T2 value is affected mainly by collagen and water content of cartilage and not very sensitive to changes in macromolecule concentration such as proteoglycan concentration [33, 34]. In addition, some pathological studies demonstrated that loss of proteoglycan is an initiating event in early OA [2], and that in the early stage of OA the amount of collagen in the framework does not seem to be severely affected [35]. Furthermore, Temple et al. suggested that the cause of age-associated cartilage deterioration depends on the age group [36]. Mosher et al. concluded that damage to the type 2 collagen matrix leads to an elevation in T2 value in persons over the age of 45 years [32]. Consequently, we can expect loss of proteoglycan prior to changes in collagen matrix contents along the pathway of asymptomatic age-related cartilage degeneration.

Considering these aspects of cartilage content degeneration, the slope of the linear regression equation describing age-related changes of T1 rho values in asymptomatic cartilage may reflect mainly the loss of proteoglycans for all age groups. On the contrary, the slope of the linear regression relating age-related change of T2 values in asymptomatic cartilage may reflect upon the degeneration of the collagen matrix and a change in water content. At young and intermediate age, assuming that the loss of proteoglycan occurred mainly in cartilage, age and T2 values are not significantly related. This observation may also explain the difference between the age-related linear change in T1 rho values and that in T2 values. Over the age of 45 years and once the degeneration of collagen matrix and change of water contents in cartilage has been initiated, there is a linear correlation between age and cartilage T2 values.

Several studies showed that cartilage T1 rho values have a larger dynamic range than cartilage T2 values. Thus they concluded that T1 rho values may be more sensitive to early cartilage degeneration than T2 values [10, 14, 15]. Our results offer information on increased cartilage T1 rho values and T2 values, and supplements previous results for detecting early OA changes that occur prior to morphological change in young to intermediate age groups. Further studies are warranted to increase the understanding of collagen content and water content in younger cartilage and the loss of proteoglycan in senescent cartilage.

Relation between weight bearing and age-related increase in T1 rho values

Morrison reported that joint contact force at the knee during walking is about three times body weight and that, when the joint is highly loaded, a greater portion of the load is transmitted through the medial condyles [37]. Similarly, Schipplein and Andriacchi reported that the medial compartment of the femorotibial joint bears 60–80% of the compressive loads in a neutrally aligned knee [38]. More recent studies demonstrated that biomechanical weakness occurs earlier in the medial femoral condyle compared with the lateral femoral condyle [36, 39]. Hence, medial knee cartilage experiences greater load than lateral knee

cartilage. Using biochemical MR imaging T2 values, Shiomi *et al.* showed that axial loading on the medial part of the joint is about three times larger than that of the lateral part of the joint and that medial cartilage T2 values are higher than those of the lateral cartilage. In addition, several articles reported higher T2 values for medial femoral and tibial cartilage than those for lateral femoral and tibial cartilage and patella cartilage [32, 41-43]. Similarly, Welch *et al.* showed that because of the difference in the respective biomechanical loading condition, T2 values for medial femoral cartilage are higher than those for patella cartilage [44].

These results indicate that T2 values differ between weight-bearing cartilage and non-weight-bearing cartilage which was tested in hypothesis two of this study. It was hypothesized that because of greater loads carried by the medial femoral cartilage compared with that carried by the lateral femoral cartilage, degeneration of proteoglycan in WB-P of medial femoral cartilage may be promoted compared with that in WB-P of lateral femoral cartilage. Indeed, T1 rho values increased more with increasing age in WB-C and WB-P than in NWB-C and LWB-P.

In medial femoral cartilage, we found a greater age-related increase in T1 rho values in WB-P than in LWB-P, while there were no differences in the age-related increase in T1 rho values between WB-P and LWB-P in the lateral femoral cartilage. To the best of our knowledge, this is the first study to evaluate the relationship between weight bearing and age-related increase in T1 rho values. Nishi *et al.* compared femoral cartilage T2 value before and after mechanical loading, and significant changes in T2 values after loading were found in only one area defined as a weight-bearing area in the medial femoral cartilage [41]. The results of that investigation agree well with the results of our study. During daily activities, such as walking, dynamic loads are greater in the medial than the lateral cartilage compartment [37, 38]. These biomechanical differences are a possible explanation of our present results. However, local mechanical cartilage stress presumably depends on the local geometry of the articulating cartilage surfaces and affects cartilage thickness, and mechanical stress in lateral knee cartilage is likely higher than that in medial knee cartilage [45-47]. These results of local cartilage contact geometry studies are in conflict with our result. It is generally accepted that both dynamic loading and cartilage on cartilage contact geometry affect knee cartilage degeneration and injures [45]. Dynamic loading conditions such as walking affect the cartilage thickness. However, local cartilage on cartilage contact geometry and its effect on cartilage is not well understood [45].

The age-related increase in T1 rho-values was greater in WB-C than in NWB-C for both medial femoral cartilage and lateral tibial cartilage. In addition, although not significant, there was a predominant trend of a greater age-related increase in T1 rho values in WB-C than in NWB-C. Hence, the results of this study showed that weight bearing appears to promote greater age-related increase in T1 rho values in cartilage *in vivo*. To the best of our knowledge, the age-related increase in T1 rho values in cartilage had not been previously assessed. Only few articles on normal cartilage investigated the correlation between weight bearing and cartilage T1 rho values *in vivo*. Stahl *et al.* divided the tibiofemoral joint cartilage into several regions and found higher cartilage T1 rho values in OA subjects than in healthy subjects. However, in that study, in both OA and healthy subjects, there was no difference in T1 rho values between weight-bearing and non-weight-bearing cartilage [14]. In addition, Carballido-Gamio reported no significant difference between weight-bearing and non-weight-bearing regions in the medial and lateral femoral compartments in OA patients [13]. Although the results of these studies are not directly comparable with the results of our study because comparisons with mild or severe OA subjects and healthy subjects were

reported, there was no evidence for higher cartilage T1 rho values in weight-bearing cartilage regions than in non-weight bearing regions. Wheaton et al. showed in an *in vitro* study that cartilage T1 rho values were strongly correlated with the magnitude of loading in cartilage [48]. Recently, it has been shown that T1 rho values are significantly higher in knee cartilage overlying bone marrow edema-like lesion (BMEL) (an area of high signal intensity in T2-weighted image and present in knee osteoarthritis and acute knee injuries, frequently associated with anterior cruciate ligament injury [12]) than in cartilage surrounding the BMEL [11,12,14,49]. A recent prospective study reported an increase in T1 rho values in cartilage overlying BMEL from baseline to follow-up [16]. In addition, Luke et al. demonstrated that after a marathon, average medial femoral cartilage T1 rho values increase and remain elevated for up to three month [50]. The results of these studies suggest that a rapid increase in load and loads exceeding normal weight bearing on cartilage may lead to increased cartilage T1 rho values and to degeneration of proteoglycan *in vivo*. Finally, these previous studies and our present study showed a trend toward more rapid age-related increase in T1 rho values in weight-bearing cartilage.

In a pathological context, the effect of weight bearing on cartilage metabolism related to proteoglycan is unclear. Several studies demonstrated that weight bearing promotes destruction and alteration of proteoglycan in cartilage directly. Sauerland et al. showed that loading alters the sulfation pattern of chondroitin sulfate of proteoglycan in cartilage and decrease normal proteoglycans concentrations [51]. Bashir et al. reported that proteoglycan concentration in medial knee cartilage is lower than that in lateral knee cartilage [52]. In addition, some studies investigated the gene suppression that is related to the decrease of normal proteoglycans concentration. Guilak et al. described that slow frequency loading generally results in suppression of proteoglycan synthesis, whereas more rapid loading frequencies stimulated synthesis [53]. Shieh and Athanasion performed high and short time loaded compression on single chondrocyte and showed a decrease in gene expression of proteoglycan [54]. In addition, using a similar approach, Pingguan-Murphy reported that they elicited a distinct and persistent chondrocyte cellular response [55]. Hence, there is uniform agreement across these studies that weight bearing of cartilage promotes the destruction and the decrease of normal proteoglycans. Consequently, greater cartilage T1 rho values would be expected for weight-bearing cartilage compared with non-weight-bearing cartilage.

However, in spite of these published articles, several authors suggested that weight bearing of cartilage leads to an increase cartilage proteoglycan synthesis or that weight bearing of cartilage does not lead to a change in cartilage proteoglycan concentration. Rogers found that in DNA genome assays higher proteoglycan concentrations in weight-bearing areas than in non-weight-bearing areas [56]. Fehrenbacher et al. showed that mRNA levels for proteoglycan, aggrecan and collagen type 2 in cartilage are significantly higher after cyclic compression on cartilage [57]. In a study comparing weight-bearing and non-weight-bearing cartilage from the same joint, Bian et al. found that between compressive deformational weight bearing and sliding-contact loading, there is no significant difference in proteoglycan synthesis, and concluded that loading does not stimulate proteoglycan synthesis [58]. Brew et al. showed that the expression of chondrocyte genes SOX9 was not influenced by the magnitude of weight bearing on cartilage [59]. Hence, while the micropathology of OA remains controversial and warrant further studies, in general, bearing weight may be associated with greater T1 rho values than not bearing weight in asymptomatic cartilage.

Limitations

In this study, no histological correlation was performed. While biochemical MRI techniques are widely accepted as accurate tool, direct measurement of proteoglycan in each region would be interesting. Furthermore, the study population of this preliminary study was relatively small, and a larger study sample would have presumably resulted in greater statistical power and the differences in the slope of the age-T1 rho value-relationship between WB-C and NWB-C might have achieved statistical significance. Next, the evaluation of T1 rho values was limited to female volunteers. There are known gender dependent differences in metabolism [60] and biomechanics [61] in cartilage. However, a previous study using T2 values shows that there is no difference between healthy male and female volunteers. Additional studies are needed to identify potential gender differences in the results of the study [62].

Finally, in our study, a significant age-related increase in T1 rho values was found not only for the medial compartment but also for the lateral compartment. However, dynamic load on cartilage alone will not explain the greater age-related increase in T1 rho values in lateral tibial cartilage and lateral femoral cartilage. Knowledge of cartilage geometry and dynamic load is required to understand the causes of greater T1 rho values the in the lateral compartment compared with those in the medial compartment. In addition, future studies on larger volunteer and patient groups are necessary to elaborate the influence of collagen content and water content on T1 rho values in younger cartilage and the influence of the loss of proteoglycan on T1 rho values in senescent cartilage. Finally, the causal relationship between the quantities of weight bearing on cartilage and the speed of proteoglycan degeneration is unclear and needs further study.

CONCLUSION

In conclusion, the results of this preliminary study contribute to our knowledge on the natural aging pathway of normal cartilage T1 rho values. The results of this study showed that T1 rho value is very sensitive to age-related cartilage degeneration and weight bearing-related degeneration prior to the appearance of morphologic changes in the cartilage. Thus, the T1 rho value may be a sufficiently sensitive and suitable biochemical MRI parameter for the early diagnosis of osteoarthritis.

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