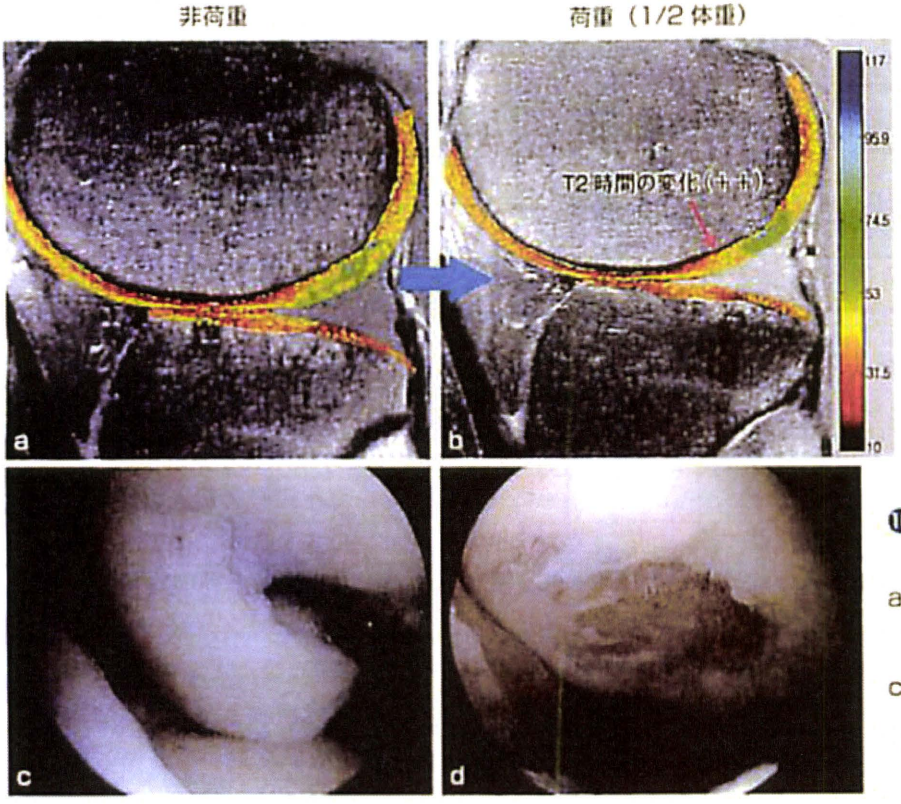

⑩ 膝関節軟骨の荷重時 MRI 解析

a, b：膝関節 3Tesla MRI を❸で示した荷重負荷にて撮像し，T2 時間で定量的解析を行った．

c, d：同一症例の膝関節鏡像．荷重 MR にて T2 時間の変化がみられた部位は，明らかに関節軟骨の異常を認めた（本文参照）．

定量的解析

MRI 撮影画像を定量評価するために，関心領域（ROI）を作製し，T1 マッピングや変位，変形などを求める（⑩）．

具体的な解析例

3 Tesla 高解像度 MRI 装置を用いて，荷重 MRI による T2 時間の変化を解析し，関節鏡像と比較した（⑩）．

外側半月板切除後の軟骨障害の例で，大腿骨外側顆部関節軟骨面に，非荷重にても関節軟骨の厚みの増大，T2 時間の異常を認め，荷重 MR にて，さらに正常ではみられない T2 時間の変化を認めた（⑩-a, b）．

関節鏡像にて大腿骨外側顆部関節軟骨面の膨隆を認め，プローブにて容易に剥離を認めた（⑩-c, d）．

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膝軟骨損傷におけるアテロコラーゲン包埋自家軟骨移植後の評価：T2 mapとdGEMRICによる初期検討［大会長賞記録］

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緒　言

関節軟骨は，細胞増殖，血流に乏しい組織であり，修復能は低い．このため，自然治癒の可能性は低く，放置しておくと損傷は増悪する．そして，損傷の悪化に伴い，関節の機能障害を来し，患者のQOL低下を招く．

このことから，様々な軟骨修復法が考案されているが，いまだにゴールドスタンダードはないのが現状である．その中で単層培養を利用した培養自家細胞軟骨移植（ACI）は良好な成績が報告され，世界各国で行われている．

単層培養による培養自家軟骨細胞移植は，骨膜でパッチした欠損部に培養軟骨細胞を浮遊液の状態で移植する方法である．

しかしながら，ACIの問題点として，①移植された軟骨細胞は三次元的空間である軟骨欠損部に均一に分布せず，偏在する可能性が高いこと，②移植された軟骨細胞は骨膜縫合部の隙間から漏出し得る可能性があること，③再生組織に最も必要な足場が存在しないことが挙げられる．

これらの問題点を克服する方法の一つとして，アテロコラーゲン包埋自家軟骨移植術がある．単層培養を用いたACIの問題を克服するためには軟骨細胞移植ではなく，軟骨細胞と基質とで三次元的に構築された軟骨様組織を移植する方が有利である．

本法は，アテロコラーゲンゲルを軟骨細胞増殖の足場とし，軟骨細胞をゲルに包埋・培養し，軟骨細胞と基質からなる組織を欠損部に移植する．アテロコラーゲン包埋移植は組織学的に良好なヒアリン軟骨によって修復されることが証明されている．

単層培養自家軟骨移植においてdGEMICを用いた移植部の評価は既に報告があるが[1),2)]，本法についての報告はまだない．

アテロコラーゲンを担体とする本法は単層培養ACIとは組織学的に異なる手法で，dGEMICおよびT_2により，移植部を評価することは臨床的に意義がある．

目　的

今回，我々はアテロコラーゲン包埋自家軟骨移植後患者について，膝軟骨移植部と健常部における造影後T_1緩和時間（T_{1post}）とT_2緩和時間（T_2）を測定し，両者を比較検討した．

キーワード　cartilage, MR imaging, Gadolinium-enhanced, T2 map, autologous chondrocyte implantation

対象と方法

1. 対象

対象は，外傷，変形性膝関節症による関節軟骨欠損でアテロコラーゲン包埋自家軟骨移植を施行した患者4例（年齢：21～44歳．男性1例，女性3例．移植後2～8年経過）である．移植部位は大腿骨内顆および膝蓋骨である．

2. 方法

撮像機種は，1.5T MR装置(Gyroscan, Philips社製)，および3T MR装置（Signa HDx, GE社製）である．撮像条件は，1.5T MRIについては，プロトン密度強調像（2D-FSE）TR/TE＝2000/18 ms, slice/gap＝3.0/0.3 mm, FOV＝16×14 cm, matrix 512×512, NEX＝2 T_1 map (2D-FSEIR)：TR/TE＝760/11.9 ms, TI＝100, 300, 500, 1000, 1500 ms slice/gap＝3.0/1.0 mm, FOV＝16×16 cm, matrix＝256×160, NEX＝1.0 T_2 map（2D-FSE)：TR/TE＝760/11.9 ms, slice/gap＝5.0/0.0 mm, FOV＝23×23 cm, matrix＝256×256, NEX＝2. 3.0T MRIについては，プロトン密度強調像（2D-FSE）TR/TE＝3500/21 ms, slice/gap＝4.0/1.0 mm, FOV＝15×15 cm, matrix 384×256, NEX＝2 T_1 map（2D-SEIR)：TR/TE＝3000/11.9 ms, TI＝#1/#2, slice/gap＝3.0/1.0 mm, FOV＝16×16 cm, matrix＝256×160, NEX＝1.0（TI＝#1；50, 100, 300, 500, 1500 ms #2；100, 300, 500, 1000, 1500 ms）T_2 map（2D-FSE)：TR/TE＝1000/7.7～61.9 ms, slice/gap＝3.0/1.0 mm, FOV＝15×15 cm, matrix＝256×160, NEX＝2. 撮像断面は，大腿骨は矢状断像，膝蓋骨は横断像で撮像した．

3. 撮像手順

撮像手順は以下のとおりである．

① 形態画像（プロトン密度強調画像）撮像．

（② 造影前 T_1 mapを撮像）

③ Gd-DTPA^{2+} 造影剤（2倍量，0.2 mmol/kg）を静注（肘窩静脈）．

④ 歩行運動（ドレッドミルにて3 km/hourの設定で10分間施行）．

⑤ 静注2時間後 T_{1post} mapを撮像．

4. T_1, T_2値の測定

T_1, T_2の測定は，アテロコラーゲンゲルおよび健常軟骨，移植部について行った．

T_1 mapは，GEYMSより提供された DT_1 mapで作成した（Fig. 1a）．T_2 mapについては，Cartigram（Functool ver 4.4, GE社製）で作成した（Fig. 1b）．

また，健常軟骨は手術，関節鏡の所見を参考に健常と判断した非荷重部軟骨とし，移植部は，手術所見，プロトン密度強調画像を参考に部位を決定した．

これらにROI（円形，2～3 mm^2）を設定し，T_1, T_2値の測定を行った．

結　　果

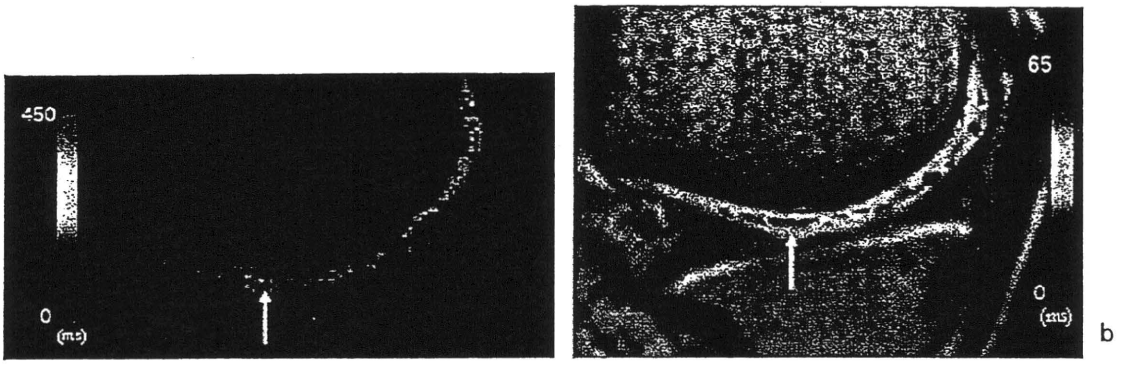
アテロコラーゲンゲルについては，T_1 (1.5T/3T)＝2262/2437 ms, T_2 (1.5T/3T)＝341/409 msであった．健常部および移植部について，T_2は，39±2.3（32～43）ms, 53±4.1 ms（41～58）であった．T_{1post}は，平均397±38 ms（324～487 ms），平均417±30 ms（366～498 ms）であった．

対応のあるt検定で，T_{1post}については両者間に有意な差は認められなかった（Fig. 2a）．T_2に関しては，健常部と移植部との間に有意差（$p=0.0006$）を認め，健常部に比べ移植部のT_2は延長傾向にあった（Fig. 2b）．

考　　察

関節軟骨のT_2は，軟骨内の含水量やコラーゲン線維のネットワークを反映しているといわれている[3)～5)]．軟骨損傷で，膠原線維ネット

2007年12月6日受理



a b

Fig. 1. 44-years-old woman with ACI
a) T_{1post} map (dGEMRIC)
b) T_2 map
T_{1post} map (a) and T_2 (b) maps for a 44-year-old female with autologous chondrocyte implantation. According to the T_{1post} map, the reparative tissue (arrow) has a GAG level comparable to that of normal tissue, while T_2 makes it possible to distinguish reparative tissue (arrow) from adjacent tissue. An elevated T_2 level is therefore believed to relate to an incomplete collagen network in the graft.
ms : milliseconds
Arrow : the graft

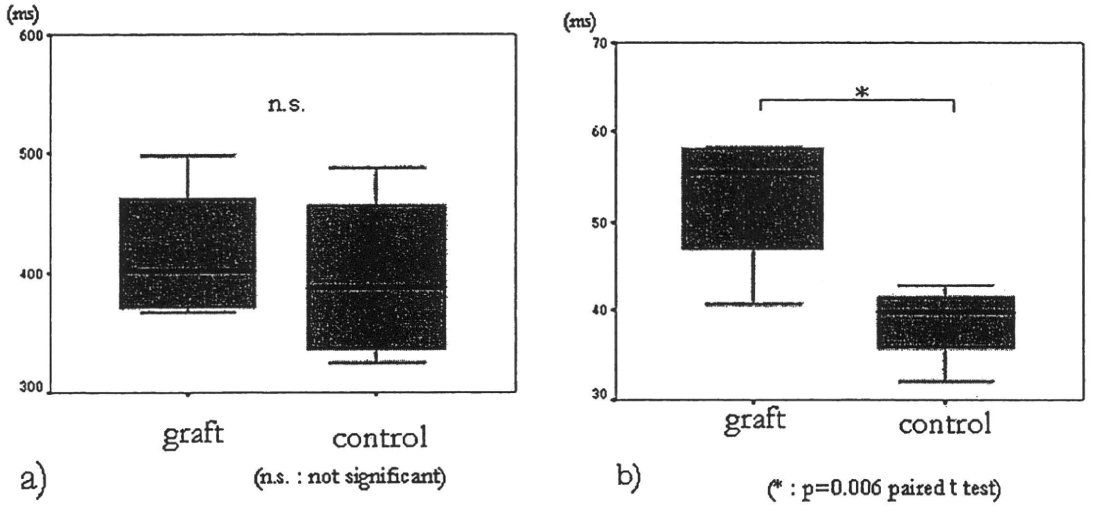


Fig. 2.
a) T_{1post} map (dGEMRIC)
b) T_2 map
The average T_{1post} values of graft and normal cartilage showed no significant difference (a). The average T_2 values showed a significant difference ($p=0.006$) (b).
ms : milliseconds

ワーク，三次元的層構造の消失や水分量の増加で，T_2は高値となる．

Glycosaminoglycan（GAG）は，プロテオグリカンの主成分で，軟骨の弾性力保持に重要な成分である．T_{1post}（造影後のT_1短縮）とこのGAG量とに一定の関係があると報告されている[6)~8)]．また，軟骨損傷で，T_{1post}は短縮するとされている．軟骨内のGAGは，負の電荷を

有するため，健常な状態では負の電荷を有し，Gd-DTPA^{2-}は相反する分布をとる．反対に損傷軟骨ではGAGは減少するため，Gdが分布するようになる．その結果，その領域のT_1短縮が生じる．

今回，T_{1post}については健常部と移植部の間に有意差がなく，両者GAG分布に差があるとはいえない．また，T_2に関しては，移植部の方が健常部よりもT_2は延長しており，軟骨の層構造，コラーゲン線維が健常部に比し乏しい，あるいは水成分が健常部に比し多いことが推定される．

以上の結果からは生検による組織所見（移植部は健常部に比べ，内部の三次元構造は異なるが，GAGの分布は近い）と類似したものとなっている．

今回の検討の問題点として，対象症例数が少ないこと，異なる磁場強度（3T, 1.5T）でのT_1値を一緒に評価していること，空間分解能等の撮像技術の問題，T_1の造影前後での変化については不詳であることが挙げられる．

今回の検討で1症例（39歳　女性；3T MRIで撮像）のみであるが，造影前T_1緩和時間（T_{1pre}）を撮像していた．その症例のT_{1post}は健常部と移植間（428 ms, 428 ms）には差がなかったが，T_{1pre}については両者間（健常部：422 ms，移植部：464 ms）で異なり，移植部のみで明らかなT_1短縮がみられた．

今回，軟骨細胞を包埋，増殖させた移植組織についてのT_1は未知であるが，アテロコラーゲンゲルのT_1の測定値から，移植組織の成熟度により健常軟骨との差は無視できないと思われた．

健常部と損傷軟骨のT_1にはほとんど差がなく，dGEMRICでは，時間の節約からT_{1pre}を省略し，T_{1post}のみを測定する[9)~11)]．一方で，Watanabeらは，造影MRによるACI後の軟骨評価では，ΔR_1（$R_{1post}-R_{1pre}$）のみがGAGと相関しており，R_{1pre}, R_{1post}は相関がなかったと報告し，ACI後の評価には，ΔR_1が重要と述べている[2)]．

以上のことから，今後は移植組織の成熟度を評価する観点から，アテロコラーゲン包埋自家軟骨移植でも，dGEMRIC（T_{1post}）に，T_{1pre}を追加する必要があると考えた．

結　　語

アテロコラーゲン包埋自家軟骨移植術後の軟骨評価について，dGEMRIC, T_2 mapを用いた初期検討を報告した．

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Delayed Gadolinium-enhanced MR to Evaluate Reparative Cartilage after Autologous Chondrocyte Implantation [Presidential Award Proceedings]

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Delayed gadolinium (Gd)-enhanced T_1 and T_2 values reflect the glycosaminoglycan (GAG) content and collagen network integrity in cartilage.

We evaluated graft integrity after autologous chondrocyte implantation (ACI) with atelocollagen by measuring T_1 and T_2 relaxation time after intravenous injection of contrast medium.

We examined 4 patients (aged 21 to 44 years) with ACI, using 1.5- and 3.0-tesla magnetic resonance (MR) scanners. Contrast medium containing Gd-DTPA was administered intravenously at double doses, subjects were made to exercise their knee joint for 10 min, and MR images were taken 2 hours after contrast injection. T_1- and T_2-calculated images were produced, and the regions of interest (ROI) were set in the reparative tissue and normal cartilage in each knee.

The average postcontrast T_1 values (T_{1post}) of graft and normal cartilage were 417 ± 30 ms and 397 ± 38 ms, which were not significantly different. The average T_2 values were 53 ± 4.1 ms and 39 ± 2.3 ms, which were significantly different ($P=0.006$). ⊿T,

The results suggest that the grafts had an almost normal GAG content, but not a normal collagen network in the cartilage.

However, we think that the maturation or integrity of the graft should be interpreted based on both the T_{1post} value and the precontrast T_1 (T_{1pre}) value of the reparative tissue because the T_{1pre} value of reparative tissue may vary with the degree of maturation or integrity.

Delayed gadolinium-enhanced MR imaging using T_1 and T_2 measurements is therefore considered a useful, noninvasive method to evaluate the graft after ACI with atelocollagen.

Original Research

Change in Knee Cartilage T2 in Response to Mechanical Loading

Takashi Nishii, MD,[1]* Kagayaki Kuroda, PhD,[2] Yuichiro Matsuoka, PhD,[2] Tomohiro Sahara, MS,[3] and Hideki Yoshikawa, MD[1]

Purpose: To assess the clinical feasibility of magnetic resonance (MR) imaging with a mechanical loading system for evaluation of load-bearing function in knee joints using cartilage T2 as a surrogate of cartilage matrix changes.

Materials and Methods: Sagittal T2 maps of the medial and lateral femorotibial joints of 22 healthy volunteers were obtained using 3.0T MR imaging. After preloading for 6–9 minutes, MR images under static loading conditions were obtained by applying axial compression force of 50% of body weight during imaging. T2 values of the femoral and tibial cartilage at the weight-bearing area were compared between unloading and loading conditions.

Results: Under loading conditions, mean cartilage T2 decreased, depending on location of the knee cartilage. For the femoral side a significant decrease in T2 with loading was observed only at the region in direct contact with the opposing tibial cartilage, in the medial femoral cartilage (5.4%, $P < 0.0005$). For the tibial side a significant decrease in T2 with loading was widely observed in the medial and lateral joint, at regions both covered and not covered by the meniscus (4.3%–7.6%, $P < 0.005$).

Conclusion: MR imaging with mechanical loading is feasible to detect site-specific changes in cartilage T2 during static loading.

Key Words: cartilage; magnetic resonance imaging; MRI T2; knee; loading
J. Magn. Reson. Imaging 2008;28:175–180.

IN EARLY CHANGES of osteoarthritis, disruption or alteration of the cartilage matrix such as a decrease in the concentration of proteoglycan and an increase in water content was shown histologically (1). Recent studies of magnetic resonance (MR) imaging assessment of joint articular cartilage have focused on qualitative assessment related to intrasubstance water content and changes in the solid matrix in order to allow sensitive and accurate evaluation of cartilage degenerative changes (2–4). In experimental studies, the T2 relaxation time (T2) of cartilage has been shown to closely correlate with collagenous architecture and water content (5–7). Clinical studies of osteoarthritis of the knee joint have confirmed the feasibility of using T2 assessment to detect early changes of osteoarthritis, and have shown that results of T2 assessment are significantly affected by patient age and osteoarthritic changes (8–10). In most clinical studies of the knee joints, patients or volunteers have been imaged supine on an imaging table without application of load-bearing force to the knee joint.

The articular cartilage in the knee joint provides a load-bearing function in conjunction with the interposed meniscus, owing to its highly organized collagen architecture and the osmotic pressure due to water flux. Failure to respond to normal load-bearing may occur due to disorder or degeneration of articular cartilage with collagen disorganization or abnormal water content, or due to tearing or degeneration of the meniscus interposed between the femoral and tibial cartilage (1,11–13). Using MR imaging, responsiveness of normal cartilage to compressive loading was investigated in experimental studies (14–16). Significant changes of cartilage thickness and signal intensity were observed in response to an increase of loading. In clinical knee imaging, dynamic response of cartilage thickness or volume, and cartilage T2 was detected after substantial loading, such as knee bending and running (6,17–19). However, there have been few studies in which cartilage T2 was directly evaluated under compressive loading to the knee cartilage using in vivo MR imaging.

We have developed a loading apparatus that applies an axial load to the knee joint during MR imaging in order to simulate the physiological load-bearing conditions of standing. The purpose of the present study, in which we used this mechanical loading system in normal volunteers, was to prospectively examine the clinical feasibility of using MR imaging to assess changes in T2 in the femoral and tibial cartilage of the knee joint.

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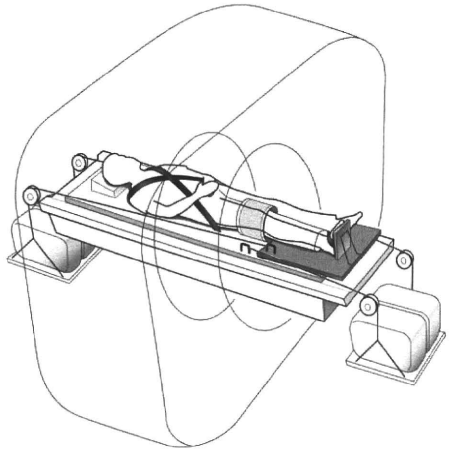

Figure 1. Schematic drawing of custom-made loading apparatus during MR imaging. Under loading conditions, axial compression force was transmitted to the knee joint cranially via the foot plate, which was connected to a water-filled weight. The same magnitude of counterforce was also applied to the backboard caudally in order to prevent cranial displacement of the body.

MATERIALS AND METHODS

Study Population

Between July 2006 and March 2007, a total of 22 healthy volunteers (9 men and 13 women) were enrolled in this study. Their mean age, weight, and body mass index (BMI) were 25 years (range, 21–43 years), 58 kg (range, 45–93 kg), and 21.4 (range, 18.0–29.7), respectively. The volunteers had no history of knee pain or stiffness, and had never undergone knee surgery. The present study protocol was approved by our Institutional Review Board. All subjects provided informed consent after receiving an explanation of the nature and procedures of the study.

MR Imaging

A unilateral knee joint of each volunteer was imaged under unloading and loading conditions using a 3.0T MR imaging scanner (Signa VH LX; GE Healthcare, Milwaukee, WI) and a home-built 14-cm transmit-receive birdcage coil. With 11 of the volunteers the left knee was imaged; with the other 11 volunteers the right knee was imaged. During MR imaging the volunteer was laid supine with the knee extended on a custom-made loading apparatus consisting of a back board and a sliding foot plate on low-friction rollers (Fig. 1). The foot of the examined leg was secured in a neutral rotational position by fixation on the foot rest of the sliding foot plate. The shoulders of the volunteer were strapped tightly to the backboard. Under loading conditions, axial compression force was transmitted to the knee joint by applying 50% of the body weight cranially via the foot plate on the examined leg. Water-filled tanks were used to deliver the force. Correlation between water volume in the tanks and actual force applied to the foot via the foot plate was confirmed by measuring the actual force with a spring balance in a preliminary examination. Simultaneously, an equal magnitude of counterforce was applied to the backboard caudally, in order to prevent cranial displacement of the body and the backboard due to compression force at the knee joint.

Under unloading and loading conditions, sagittal T2 maps were obtained from a multiple spin echo sequence with the following parameters: repetition time, 1500 msec; eight evenly spaced echo times from 15–120 msec; slice thickness, 3 mm; field of view, 12 cm; matrix, 512 × 256 (in-plane resolution of 0.23 × 0.47 mm) interpolated to 512 × 512 (in-plane resolution of 0.23 × 0.23 mm); two signals acquired for a total time of 13 minutes. The frequency-selective fat-suppression technique was used to minimize chemical shift artifact at the cartilage–bone interface. Frequency encoding was oriented in the cranial-to-caudal direction. At each of the medial and lateral femorotibial joints, one sagittal image passing through the center of the femoral condyle was obtained. In this imaging plane the femoral and tibial articular cartilage in the weight-bearing area consisted of cartilage covered by the anterior meniscus, cartilage in contact with the opposing articular cartilage, and cartilage covered by the posterior meniscus (Fig. 2a).

First, MR images under unloading conditions were acquired and then the load was applied for an average of 8 minutes (range, 6–9 minutes), after which MR images under loading conditions were obtained. Between imaging under unloading and loading conditions, rotational change of the knee was minimized by firmly fixing the foot to the foot plate. The imaging planes were coregistered by comparing the positions on the axial localizing images under unloading and loading conditions. After MR imaging none of the volunteers complained of knee or hip pain that could be attributed to the loading apparatus.

Data Analysis

Each T2 value was calculated on a pixel-by-pixel basis by fitting the echo time data and the corresponding signal intensity to a mono-exponential equation. The first echo of the multiecho sequences was excluded in calculation of T2, to minimize T2 inaccuracy due to stimulated echoes (8,10,17,20). On each medial and lateral sagittal image, three regions of interest (ROIs) in the femoral and tibial cartilage in the weight-bearing area were manually defined for each subject (Fig. 2b). The ROIs of the femoral cartilage were designated Z1 (covered by the anterior meniscus), Z2 (in direct contact with the opposing tibial cartilage), and Z3 (covered by the posterior meniscus). The ROIs of the tibial cartilage were designated Z4 (covered by the anterior meniscus), Z5 (in direct contact with the opposing femoral cartilage), and Z6 (covered by the posterior meniscus). The thickness of the femoral and tibial cartilage was calculated at the center of each zone. The bone–cartilage interface and cartilage surface were determined manually by referring to the intensity profile curve along the cartilage depth. The ROIs and cartilage thickness were defined on the image corresponding to the first echo of the multiecho series. Definitions of ROIs and calculation of cartilage thickness were repeated three times by a single observer (T.N.), with more than 10 years of

Table 1
Reproducibility of Measurements in Cartilage Thickness and T2 at Each ROI in the Medial and Lateral Femorotibial Joint

Zone	Cartilage Thickness		Cartilage T2	
	Medial Joint	Lateral Joint	Medial Joint	Lateral Joint
Z1	4.5%	5.6%	3.5%	4.2%
Z2	4.9%	3.9%	2.7%	2.2%
Z3	3.6%	5.1%	4.9%	1.8%
Z4	5.0%	5.5%	3.3%	3.9%
Z5	3.5%	4.9%	2.7%	3.2%
Z6	3.8%	4.5%	3.6%	3.5%

experience in the study of articular cartilage imaging, and the T2 values of each ROI and cartilage thickness value were averaged. Analysis of T2 values was performed using Beth Israel Deaconess Medical Center software for functional imaging of cartilage (Boston, MA), and calculation of cartilage thickness was performed using three-dimensional image analysis software (Virtual Place; AZE, Tokyo, Japan).

To assess the reproducibility of the T2 measurements, two consecutive MR datasets were acquired from each of five normal volunteers (age range, 20–26 years; all female) under unloading conditions. Between these MR imaging sets the volunteers were removed from the imaging table and repositioned. The reproducibility of cartilage thickness and T2 at each ROI was calculated as the coefficient of variation (standard deviation/mean ×100 [%]), and the mean reproducibility was calculated as the root means square average for each volunteer.

The reproducibility of cartilage thickness measurements at each ROI ranged from 3.5%–5.0% in the medial joints and ranged from 3.9%–5.6% in the lateral joint (Table 1). The reproducibility of T2 measurements at each ROI ranged from 2.7%–4.9% in the medial joints and from 1.8%–4.2% in the lateral joint (Table 1).

Cartilage thickness and T2 values under unloading and loading conditions in each ROI were compared using a paired *t*-test. Changes in T2 with loading were compared between male and female volunteers using the nonparametric Mann–Whitney *U*-test. The relationships between changes in T2 with loading and the age and BMI of volunteers were evaluated using the Spearman correlation coefficient. In each ROI, correlation between changes in T2 and changes in cartilage thickness with loading was examined using the Spearman correlation coefficient. A probability value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Changes in Cartilage Thickness (Table 2)

Under loading conditions, all ROIs except Z3 in the medial joint showed a decrease of mean cartilage thickness, ranging from 0.5%–7.3% of the initial cartilage thickness under unloading conditions. For the femoral side, there was a significant decrease of thickness with loading at Z2 in the lateral joint ($P < 0.01$). For the tibial side, there was a significant decrease of thickness with loading at Z4 in the medial joint ($P < 0.01$), and Z4 and Z5 in the lateral joint ($P < 0.05$). There was no significant relationship between changes in cartilage thickness and the gender, age, or BMI of volunteers.

Changes in Cartilage T2 (Table 3)

Under loading conditions, cartilage T2 tended to decrease, especially at the tibial side (Fig. 3). On the femoral cartilage, a mean decrease of T2 by 2% or more under loading was seen only at Z2 in the medial joint, whereas all ROIs on the tibial cartilage showed a mean decrease of T2 by 2% or more under loading. For the femoral side there was a significant decrease in T2 with loading at Z2 in the medial joint ($P < 0.0005$). For the tibial side there was a significant decrease in T2 with loading at Z5 and Z6 in the medial joint ($P < 0.01$), and Z4 and Z5 in the lateral joint ($P < 0.05$). On an individual basis, a decrease of T2 was seen in 11 knees (50%) at Z1, 18 knees (82%) at Z2, 13 knees (59%) at Z3, 13 knees (59%) at Z4, 19 knees (86%) at Z5, and 16 knees (73%) at Z6 in the medial joint. In the lateral joint, a decrease of T2 was seen in 12 knees (55%) at Z1, 14 knees (64%) at Z2, 10 knees (46%) at Z3, 14 knees (64%) at Z4, 17 knees (77%) at Z5, and 14 knees (64%) at Z6. There was no significant relationship between changes in T2 with loading and the gender, age, or BMI of volunteers. In each ROI a change in T2 with loading was not significantly correlated with change in cartilage thickness with loading.

DISCUSSION

Structural and compositional properties of articular cartilage play an important role in the load-bearing

Table 2
Cartilage Thickness of Each ROI (Mean ± SD) in the Medial and Lateral Femorotibial Joint Under Unloading and Loading Conditions

Zone	Medial Joint				Lateral Joint			
	Unloading (mm)	Loading (mm)	Change* (%)	*P*-value	Unloading (mm)	Loading (mm)	Change* (%)	*P*-value
Z1	1.4 ± 0.3	1.4 ± 0.4	−1.5 ± 12	0.9	1.3 ± 0.4	1.3 ± 0.4	−0.5 ± 10.3	0.6
Z2	1.7 ± 0.4	1.6 ± 0.4	−2.8 ± 8.6	0.2	1.5 ± 0.4	1.4 ± 0.3	−7.3 ± 13.6	<0.01
Z3	2.2 ± 0.5	2.2 ± 0.6	1.1 ± 12.0	0.7	2.3 ± 0.5	2.2 ± 0.5	−3.1 ± 7.5	0.07
Z4	1.6 ± 0.3	1.5 ± 0.3	−5.3 ± 7.8	<0.01	1.2 ± 0.4	1.1 ± 0.5	−5.9 ± 9.5	<0.05
Z5	1.8 ± 0.3	1.8 ± 0.2	−2.2 ± 7.7	0.3	2.7 ± 0.5	2.5 ± 0.6	−4.9 ± 8.1	<0.05
Z6	2.2 ± 0.5	2.1 ± 0.5	−4.2 ± 11.4	0.06	3.4 ± 0.8	3.3 ± 0.8	−3.1 ± 9.3	0.1

*Changes were calculated as (thickness on loading condition − thickness on unloading condition/thickness on unloading condition × 100.

Table 3
T2 Values of Each ROI (Mean ± SD) in the Medial and Lateral Femorotibial Joint Under Unloading and Loading Conditions

Zone	Medial Joint				Lateral Joint			
	Unloading (ms)	Loading (ms)	Change* (%)	*P*-value	Unloading (ms)	Loading (ms)	Change* (%)	*P*-value
Z1	48.4 ± 4.8	48.4 ± 6.0	1.1 ± 9.0	0.6	52.4 ± 6.0	52.6 ± 5.9	1.0 ± 11.3	0.9
Z2	50.2 ± 4.5	47.4 ± 3.9	−5.4 ± 5.5	<0.0005	50.1 ± 5.1	49.4 ± 4.9	−1.1 ± 6.2	0.3
Z3	48.5 ± 3.8	47.7 ± 3.4	−1.5 ± 6.3	0.2	48.8 ± 4.2	48.9 ± 4.3	0.3 ± 5.7	0.9
Z4	48.1 ± 5.0	47.1 ± 5.9	−2.2 ± 7.0	0.2	53.9 ± 5.7	51.3 ± 5.5	−4.3 ± 10.1	<0.05
Z5	50.4 ± 5.3	46.4 ± 4.1	−7.6 ± 6.0	<0.0001	53.3 ± 6.3	52.4 ± 6.4	−5.3 ± 4.7	<0.0001
Z6	48.1 ± 5.4	45.7 ± 4.9	−4.6 ± 8.0	<0.01	51.8 ± 6.5	50.0 ± 5.8	−3.2 ± 7.3	0.06

*Changes were calculated as (T2 value on loading condition − T2 value on unloading condition)/T2 value on unloading condition × 100.

function of the knee joint (13). The macromolecular framework of normal cartilage, which consists of highly organized collagen fibrils, proteoglycans, and interstitial water, is strongly stress-resistant in response to applied load. The fluid pressurization of cartilage makes a great contribution to this stress-resistance due to the hydrodynamic pressure; however, the responsiveness of fluid pressure strength is dependent on the water content and permeability of the solid matrix. The low water permeability of normal cartilage provides a high hydrodynamic force in response to applied load. The increased water content and high water permeability that are associated with early degenerative changes in cartilage result in weakening of the stress-resistance of the fluid pressure, and may promote degenerative changes in the sold cartilage matrix (13). Therefore, evaluation of dynamic changes in the collagenous architecture, along with evaluation of water influx or efflux through cartilage in response to physiological loading, may provide more sensitive and detailed assessment of degenerative pathological change and load-bearing function of cartilage than mere static assessment of the solid matrix and water content.

Previous experimental studies indicate that cartilage T2 allows reliable, noninvasive assessment of collagenous content and architecture (7), depletion of proteoglycan (5), and changes in water content (21). Clinical studies of knee imaging in vivo confirm that T2 is a feasible means of detecting spatial variation in cartilage depth (8), effects of patient age (8,10), and involvement of osteoarthritis (9), presumably due to the fact that T2 reflects the content and distribution of interstitial water or the solid matrix. Recently, investigators have studied dynamic response of cartilage solid matrix or interstitial water after substantial loading of the knee joint (6,17,22). Liess et al (6) studied recovery of T2 in patellar cartilage of healthy volunteers after a repeated knee bending exercise; after 45 minutes of rest, cartilage thickness had increased by 5.4% and T2 had increased by 2.6%, compared with assessment immediately after the exercise. Mosher et al (17) assessed T2 in the femorotibial cartilage of healthy volunteers before and after 30 minutes of running and found a significant decrease in T2 of the superficial femoral cartilage after running. To the best of our knowledge, there has been only one study (Nag et al (22)) in which the effect of compressive loading on cartilage T2 was directly evaluated. That study showed a significant decrease in T2 of the femoral

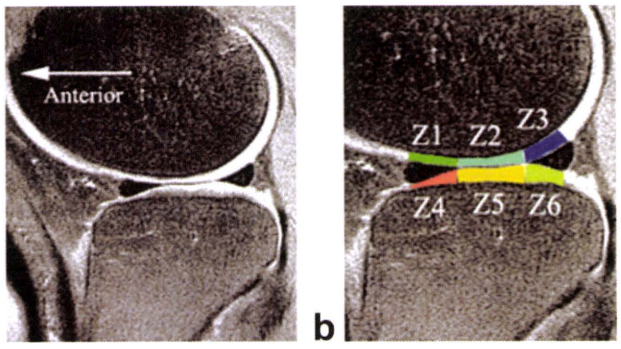

Figure 2. (a) Representative sagittal MR image (1500/15) of the lateral femoral-tibial joint, and **(b)** definition of regions of interest (ROIs) in the femoral and tibial cartilage in the weight-bearing area.

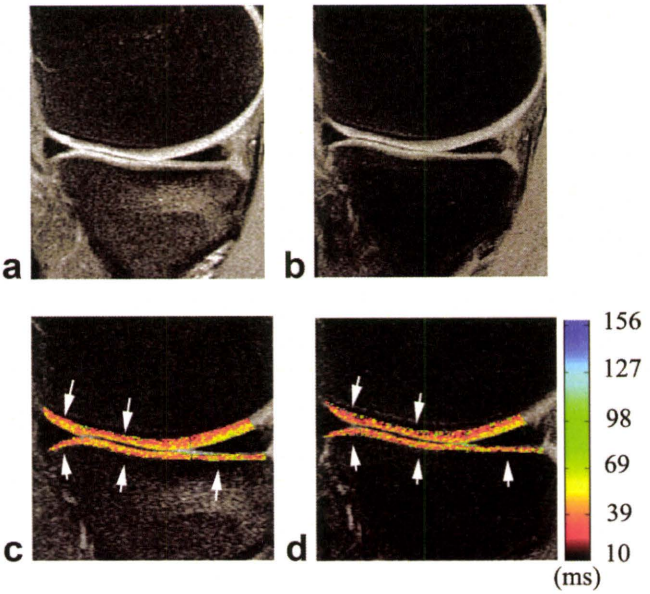

Figure 3. MR images and T2 maps of cartilage in the medial femorotibial joint of a 22-year-old female volunteer. **a,b:** Sagittal MR images (1500/15) under unloading and loading conditions. There was no significant difference in cartilage thickness between unloading and loading conditions. **c,d:** T2 maps of the cartilage in the examined ROIs under unloading and loading conditions. On the color-coded T2 map a low T2 value is represented by red color and a high T2 value is represented by green or blue color. Under loading conditions a decrease in T2 was observed in the femoral and tibial cartilage (arrows).

cartilage with in situ mechanical loading during MR imaging. However, the imaging performed in that study was of rather low resolution (≈0.6 mm; 1.5T MR imaging) for evaluation of relatively thin femoral and tibial cartilage, the thickness of which ranges from 1–3 mm. The limited resolution in that study may have led to its relatively high standard deviation in T2 values of >10 msec at each ROI, compared with standard deviation in other previous studies for T2 values of <5 msec (6,23).

The present findings demonstrate the clinical feasibility and importance of MR imaging under mechanical loading for direct evaluation of response of T2 in femoral and tibial cartilage. Sufficient image quality with high in-plane resolution (0.23 mm) was obtained in the assessment of cartilage T2, probably due to the superior performance of the 3.0T MR imaging scanner, the two-signal averaging, and the home-built knee coil. We consider that this image quality and the ability to maintain an unchanging foot position using the fixation device contributed to our obtaining an acceptable reproducibility error of cartilage thickness and T2 measurements, which are comparable to results obtained in previous studies (6,23). With application of loading, we detected significant decreases in cartilage thickness and T2 values, which were greater than the reproducibility errors, especially in the tibial cartilage. This finding of decreased T2 in response to compressive loading is consistent with previous experimental (14,24) and clinical studies (6,17,22). Decreased T2 on loading has previously been accounted for by deformation of cartilage architecture, extrusion of water content, and relative increase of proteoglycan and collagen content within the cartilage (6,14,15,17,22). In daily activities such as standing and walking, the articular cartilage in the knee joint is subject to loading conditions that are considerably different from those of resting and supine positions. The present findings suggest that MR imaging under mechanical loading is a useful diagnostic tool for assessment of articular cartilage under physiological conditions during daily activities.

In the present assessment of cartilage T2, ROIs in the weight-bearing area were defined according to whether they were covered by the meniscus, in consideration of the important mechanical role of the load-bearing function of the meniscus. In cadaveric studies under loading conditions, the compressive load transmitted through the meniscus was greater than the compressive load on the uncovered cartilage, and the meniscus was assumed to distribute the load transmission over the entire surface of the tibial cartilage, thus preventing excessive stress on the exposed cartilage (12,13). In the femoral cartilage, the present results showed significant changes in T2 only in the area not covered by the meniscus, while significant changes in T2 were widely observed in areas covered by the meniscus and areas not covered by the meniscus on the tibial cartilage. Given previous experimental findings in which T2 significantly correlated with biomechanical properties such as cartilage stiffness (5,25), these present findings may reflect location-specific load transmission patterns associated with the meniscus in normal knees. In this context, T2 evaluation under loading conditions can be expected to provide biomechanical assessment of pathological conditions with respect to localized stress concentration in the cartilage, due to degenerative or traumatic meniscus disorders, or abnormal knee alignment such as varus/valgus deformity or flexion contracture.

We evaluated the response of cartilage thickness and T2 after preloading for an average of 8 minutes. Herberhold et al (16) studied deformational behavior of the articular cartilage under static loading of 150% of the body weight with femoropatellar knee imaging ex vivo; the deformations of the patellar and femoral cartilages after 8 minutes of compression were 25%–30% of the final deformations of those cartilages after 214 minutes of compression. Although the location of the cartilage and magnitude of compression force differed from that report, our results may represent relatively early response of the knee cartilage under static loading, simulating the status of the articular cartilage in the physiological standing position for a relatively short period. In the biphasic theory of time-dependent compressive creep and stress-relaxation behavior of cartilage (26), exudation of interstitial fluid occurs first after loading, providing frictional drag of the fluid through the solid matrix. As fluid is excluded from the tissue, deformation of the cartilage occurs. Therefore, an absence of correlation between change of T2 and change of cartilage thickness with loading in the present study may be partly accounted for by the inconsistent behavior of interstitial fluid flux and deformation of the cartilage under compression force.

The present study has several limitations. First, we manually defined the cartilage boundary and ROIs in our calculation of cartilage thickness and T2; use of automatic or semiautomatic computational procedures might have improved the reproducibility of our measurements. However, cartilage boundary was easily detected in the present study, presumably due to the relatively high in-plane resolution, high signal contrast between the cartilage and adjacent subchondral bone, and use of the anterior and posterior meniscus as an anatomical landmark. Given the acceptable reproducibility of the present measurements of cartilage thickness and T2, we concluded that the present cartilage boundary and ROIs were reasonably well defined. Second, assessment of average T2 values of bulk ROIs from the cartilage base to the articular surface may be insufficiently sensitive to detect small T2 changes in a restricted region, although the present results show significant differences between T2 with compressive loading and T2 without compressive loading. The use of other quantitative methods such as comparison of T2 profile curves as a function of normalized distance from the bone/cartilage interface to the cartilage surface, which has been used in other studies (8,17,20), may allow more detailed assessment of effects of compressive load on cartilage. Third, in our preliminary trials we used 50% of body weight as the maximal tolerable load during MR imaging under loading conditions, assuming that this would simulate loading conditions in the static standing position on both legs. However, it is unclear how accurately this system simulated the mechanical environment in the physiological standing position, because it did not incorporate surrounding mus-

cle action such as contraction of the quadriceps or hamstrings or forces from surrounding ligamentous restraints. Furthermore, in the present study we did not investigate whether cartilage T2 on loading changed linearly or nonlinearly according to the magnitude of the compression load, or whether decreased T2 returned to the baseline value after relief of mechanical loading. Further studies of T2 assessment with different magnitudes of compression load and reevaluation after relief of loading are needed to elucidate the comprehensive load transmission mechanism with respect to various meniscus-articular cartilage combinations and the biphasic load-supportive function of the solid matrix framework and hydrodynamic pressure of interstitial fluid. Finally, the aim of the present study was to examine the feasibility of T2 assessment using a mechanical loading device, and the number of volunteers was small, and the volunteers were predominantly young (≤43 years of age). Although previous reports indicate that cartilage thickness and T2 in the knee joint is significantly affected by age (8,10,27), we did not detect an effect of age on changes in cartilage T2 in response to dynamic loading in the present study, due to the limited deviation of subject age. Clarification of this issue will require further studies with larger numbers of subjects in various age brackets.

In conclusion, the present findings indicate that it is clinically feasible to use T2 assessment with a mechanical loading apparatus to examine load response of articular cartilage in the knee joint. Although further studies are needed, T2 evaluation under loading may allow detection of early degenerative changes of the cartilage and meniscus with high sensitivity, and provide biomechanical assessment of pathological conditions related to localized stress concentration in the cartilage.

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Evaluation of cartilage matrix disorders by T2 relaxation time in patients with hip dysplasia

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Summary

Objective: Early detection of cartilage disorder in dysplastic hips is important in predicting subsequent progression of osteoarthritis and determining the appropriate timing of osteotomy surgery. We assessed the feasibility of T2 assessment using magnetic resonance (MR) imaging at 3 T for evaluating early changes in the acetabular and femoral cartilages for patients with hip dysplasia.

Methods: Sagittal T2 maps of the hip were obtained using 3 T MR imaging in 10 normal volunteers (14 hips) and in 23 patients (26 hips) with hip dysplasia at pre-arthritic stage (without osteoarthritis) or early-arthritic stage (with osteoarthritis at the Kellgren–Lawrence system of grade 1 or 2). T2 values and the visual appearance of T2 mapping, including gradient T2, low T2, and high T2 patterns, were compared at the superior zones of the acetabular and femoral cartilages among the normal, pre-arthritic, and early-arthritic groups.

Results: There were no significant differences in T2 values for both cartilages among the three groups. Regarding the visual appearance of T2 mapping for the acetabular cartilage, all hips in the normal group showed a gradient T2 pattern, while the pre-arthritic groups included six hips (43%) with a low T2 pattern, and the early-arthritic group showed either a low T2 pattern (33%) or a high T2 pattern (67%). The frequency of the gradient T2 pattern was significantly lower for dysplastic hips than for normal hips, in the acetabular and femoral cartilages ($P < 0.05$).

Conclusions: This preliminary study demonstrated the clinical feasibility of T2 assessment of hip cartilage using 3 T MR imaging. T2 mapping classification may enable the early detection of osteoarthritic degeneration and the detection of developmental disorders of cartilage matrix in patients with hip dysplasia.

Key words: Hip dysplasia, MR imaging, Cartilage, T2 relaxation time, Osteoarthritis, Cartilage matrix.

Introduction

Hip dysplasia is one of the major causes of hip osteoarthritis[1,2]. Radiological evidence of dysplasia in hips without osteoarthritis is shown as a risk factor for the development of hip osteoarthritis in a prospective study[3]. Hips with moderate or severe degrees of dysplasia are likely to deteriorate progressively and eventually develop into terminal osteoarthritis with persistent symptoms and severely impaired function[4]. When effective surgical treatment such as osteotomy surgery is applied before osteoarthritic changes progress, reliable outcomes can be expected, with the prevention of osteoarthritic changes; however, delay of treatment following osteoarthritic involvement often results in unsatisfactory outcomes[5]. Early detection of cartilage disorders in dysplastic hips is important in predicting the subsequent progression of osteoarthritis and determining appropriate timing for osteotomy surgery.

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Several imaging modalities are currently available to evaluate osteoarthritis of the hip, including plain radiography, arthrography, bone scintigraphy[6], computed tomography (CT) arthrography[7], and magnetic resonance (MR) imaging with and without arthrographic effect[8,9]. Plain radiography is widely used for diagnosis and assessment of the severity of joint osteoarthritis, and showed significant correlation with hip cartilage thickness and volume[10]; however, several other reports have proposed inaccurate relationships between radiographic findings and the status of the articular cartilage[11,12]. Recent investigations using CT arthrography[7] and MR imaging with and without arthrographic effect[7–9] achieved excellent visualization and sensitive detection of morphological changes in hip cartilage (thinning or defect); however, the diagnostic abilities of these modalities are limited for early cartilage disorders without change of cartilage thickness or volume, such as softening and surface fibrillation[7]. Disruption or alteration of the cartilage matrix such as a decrease in the concentration of proteoglycan and an increase in water content is found histologically in early changes of osteoarthritis[13]. It may be more effective to image cartilage matrix disorders or water content than to image cartilage morphological changes such as thickness and shape in detecting early changes of cartilage disorders with high sensitivity and accuracy.

MR imaging techniques that have been proposed for sensitive evaluation of cartilage matrix changes include T2 relaxation time (T2), delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC), and T1 in the rotating frame (T1rho)[14]. Evaluation of T2 of the articular cartilage shows great potential for the quantitative assessment of collagen and water content[15,16] and indicates clinical usefulness for knee imaging *in vivo*[17,18]; however, to the best of our knowledge there have been no reports that assess hip cartilage by T2. This is because of difficulties involved in obtaining satisfactory image quality and in differentiating between the acetabular and femoral cartilages.

MR imaging at higher magnetic field strength (at 3 T or more) may provide improved image quality of the hip cartilage due to superior signal-to-noise contrast[19]. The objective of the present study is to assess the feasibility of T2 evaluation using MR imaging at 3 T in detecting early changes in the acetabular and femoral cartilages in patients with hip dysplasia.

Materials and methods

Ten normal volunteers (14 hips) and 23 patients with hip dysplasia (26 hips) were included in this study. Because patients with hip dysplasia are predominantly female[20], men were excluded from the study to prevent the potentially confounding influence of sex difference on T2 in the articular cartilage[21]. Exclusion criteria for volunteers were present and/or past experience of hip pain, stiffness, or gait disability. Hip dysplasia was defined by center-edge angle of Wiberg of 24° or less[22] on anteroposterior radiographs. Inclusion criteria for dysplastic hips to the study were as follows: no previous hip surgery, Class I subluxation (less than 50%) according to the classification of Crowe *et al.*[23], and radiological osteoarthritis classification according to the Kellgren–Lawrence system[24] of grade 0 (no osteoarthritic finding), grade 1 (possible narrowing of joint space and/or osteophytes), or grade 2 (definite narrowing of joint space, definite osteophytes, and slight sclerosis). In the present study, osteoarthritis classification of grade 0 with radiological evidence of hip dysplasia was categorized as pre-arthritic stage, and grade 1 or 2 as early-arthritic stage. Institutional review board approval was obtained for this study, and all patients provided informed consent after the nature of the procedure had been fully explained.

The average ages of the volunteers and patients were 34 years (range, 23–51 years) and 40 years (range, 22–69 years), respectively. The average heights and weights were 163 cm (range, 153–171 cm) and 54 kg (range, 47–80 kg) in the volunteers, and 157 cm (range, 149–163 cm) and 53 kg (range, 42–80 kg) in the patients, respectively. The center-edge angle of the patients ranged from −20° to 24° (mean, 6.5°); there were 14 hips at the pre-arthritic stage (grade 0) and 12 hips at the early-arthritic stage (eight hips at grade 1 and four hips at grade 2). Patients had no pain in six hips and slight or moderate pain either while walking or after a long walk in 20 hips. The six asymptomatic hips were diagnosed as hip dysplasia during examination of the opposite symptomatic hips.

MR imaging of the hip was performed on a Signa 3 T MR scanner (GE Healthcare, WI, USA) using a flexible surface coil. The volunteers and patients were positioned supine with the hip in neutral position. Two-dimensional dual-echo spin-echo images were obtained with the following parameters: repetition time/echo time 1500 ms/10 and 45 ms; field of view 16 cm; matrix 512 × 256 interpolated to 512 × 512 with a resulting in-plane pixel resolution of 312.5 μm; 5 mm slice thickness, and two signals acquired for a total time of 13.5 min. Frequency encoding was head to foot across the hip joint, and the fat-suppression technique was used to minimize chemical shift artifact at the bone/cartilage interface. A single sagittal image passing through the center of the femoral head was obtained. When the imaging plane was lateral to the outer edge of the acetabular rim in the coronal scout view, the imaging plane was moved medially to be located within the acetabular rim. The sagittal plane was employed because cartilage disorder is often observed at the anterosuperior region of the acetabulum in arthroscopic studies of dysplastic hips[25]. A single slice sequence was used to prevent inaccuracy of T2 measurement caused by magnetization transfer contrast from off-resonance radiofrequency irradiation found in multi-slice sequences[26,27].

The acetabular and femoral cartilages were manually segmented on the mid-sagittal image and the T2 value was calculated assuming a single exponential decay component. A color-coded T2 map of the cartilage was overlaid on the mid-sagittal image; low T2 values were represented in red while high T2 values were colored green or blue (Fig. 1). Regions of interest (ROIs) in the acetabular and femoral cartilages were defined at the weight-bearing area of the superior 20° range of the cartilage, from the cartilage surface to the basal area, and the average T2 value and visual appearance of T2 mapping within the ROIs were evaluated. The visual appearances of T2 mapping were classified into three patterns (Fig. 2): "gradient T2 pattern" for low T2 values at the deep cartilage area and high T2 values at the superficial cartilage area, which was considered representative of the spatial variation of normal knee cartilage[28]; "low T2 pattern" for ROIs occupied predominantly by low T2 values up to the superficial cartilage area; and "high T2 pattern" for ROIs occupied predominantly by high T2 values even at the deep cartilage area. On assessment for each case, representative cases of the three mapping patterns (Fig. 2) were used as the reference atlas. Definitions of the ROIs were repeated three times by a single observer (TS) without knowledge of presence of hip dysplasia or the radiological osteoarthritis classification, and the T2 values of the ROIs were averaged. Inter-observer reliability between two observers (TN, TS) was assessed in the first 10 subjects, with a coefficient of variation of 2.5% for the acetabular ROI and 3.8% for the femoral ROI. Visual appearance of T2 mapping was interpreted blindly by two observers (TN, TS) independently without knowledge of presence of hip dysplasia or the radiological osteoarthritis classification. In general (95% of the cases in the acetabular cartilage and 93% of the cases in the femoral cartilage), there was agreement between the two observers. In the remaining cases, a consensus of opinion was obtained between the two observers. All imaging analysis was conducted using Beth Israel Deaconess Medical Center software for functional imaging of cartilage (Boston, MA, USA).

Clinical symptoms of the hip were evaluated using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC)[29] pain score at the time that MR imaging was conducted. When both hips were examined, WOMAC questionnaires were taken separately for the right and left hips. The WOMAC pain score was calculated as a summation of the scores ranging from 0 (no pain) to 4 (extreme pain) in response to each of five items (range of possible total score 0–20). T2 value and the visual appearance of T2 mapping for each ROI were compared among the normal,

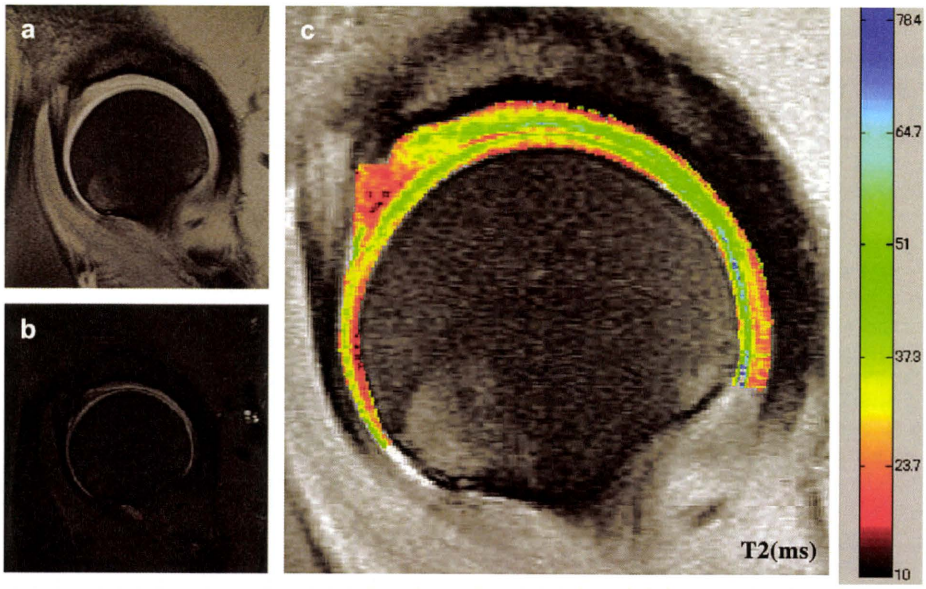

Fig. 1. Representative mid-sagittal MR images of a normal volunteer hip (a: 1500/10 ms, b: 1500/45 ms), and corresponding T2 map overlaid on the cartilage region (c). Superior and anterior directions of the hip are toward the top and left of each image, respectively.

pre-arthritic, and early-arthritic hips, using analysis of variance and the Fisher exact test. They were also compared between asymptomatic and symptomatic hips, using the nonparametric Mann–Whitney *U* test and the Fisher exact test. Between normal hips and dysplastic hips, and between asymptomatic hips and symptomatic hips, we calculated a sample size to detect a 10% difference of T2 value based on a previous report comparing T2 value in healthy knees and osteoarthritic knees[18]. Fourteen hips or more in each group were sufficient to determine whether there was a significant difference (power > 0.8, $P < 0.05$). The relationship between WOMAC pain scores and T2 values was evaluated using the Spearman correlation coefficient. A P value of less than 0.05 indicated significance.

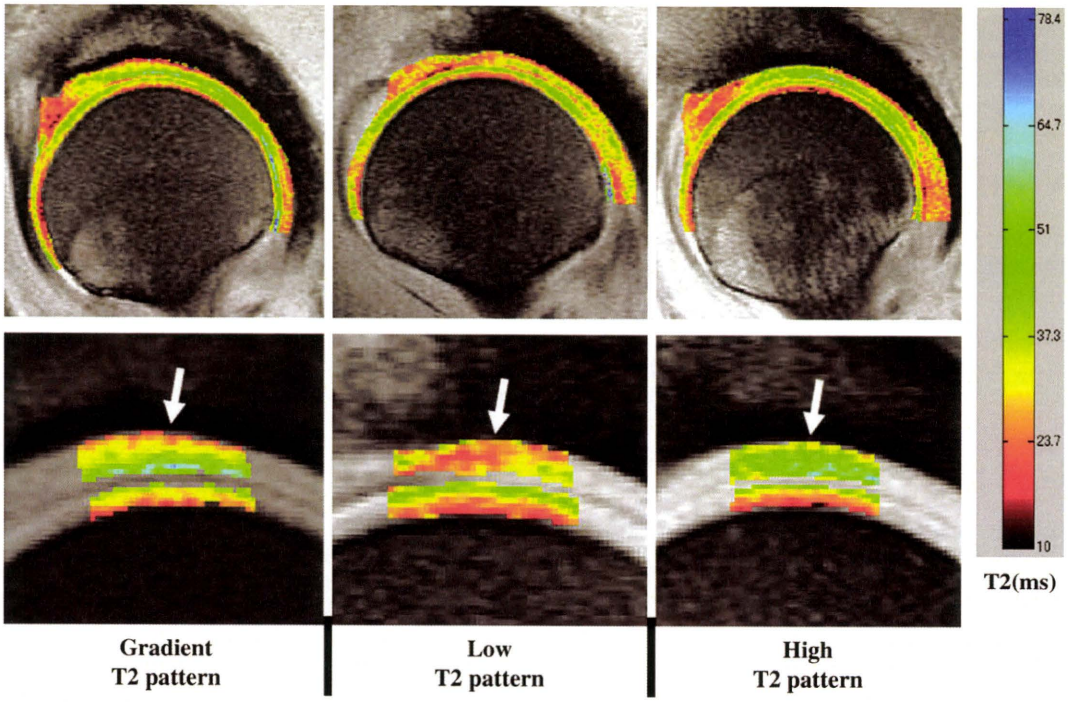

Fig. 2. Representative cases for the three patterns in visual appearance of T2 mapping (upper image) and their magnified images of the weight-bearing area with segmentation of the ROIs in the acetabular and femoral cartilages (lower image). Note T2 distribution within the ROIs of the acetabular cartilage (arrows). Gradient T2 pattern shows low T2 at the deep cartilage area and high T2 values at the superficial cartilage area; low T2 pattern shows predominantly low T2; and high T2 pattern shows predominantly high T2.

Results

The average ages of the normal, pre-arthritic, and early-arthritic groups were 34 years (range, 23–51), 35 years (range, 22–50), and 45 years (range, 23–69), respectively. The mean height/weight of the three groups were 163 cm/54 kg, 156 cm/50 kg, and 157 cm/55 kg, respectively; there was no statistical difference of age and weight among the three groups, however, height of the normal group was significantly higher than the other two groups ($P < 0.05$). All hips in the normal group, four hips in the pre-arthritic group, and two hips in the early-arthritic group showed no pain, while the other 10 hips in the pre-arthritic group and 10 hips in the early-arthritic group showed slight or relatively mild pain with WOMAC pain scores ranging from 1 to 12 points.

There was no significant difference in T2 value at the defined superior ROI of the cartilage among the normal, pre-arthritic, and early-arthritic groups, both for the acetabular and femoral sides. On the acetabular cartilage ROI, the mean T2 values $\pm$ 1 standard deviation for the normal, pre-arthritic, and early-arthritic groups were 33.4 ms $\pm$ 4.5, 32.0 ms $\pm$ 3.9, and 37.1 ms $\pm$ 12.0, respectively. On the femoral cartilage ROI, these values were 29.4 ms $\pm$ 3.0, 29.0 ms $\pm$ 4.4, and 28.0 ms $\pm$ 3.7, respectively.

The visual appearance of T2 mapping for the acetabular ROI showed a different distribution of the three patterns among the normal, pre-arthritic, and early-arthritic groups (Fig. 3). On the acetabular ROI, all hips in the normal group demonstrated gradient T2 pattern, while six hips in the pre-arthritic group (43%) and four hips in the early-arthritic group (33%) demonstrated low T2 pattern. The remaining eight hips in the early group (67%) demonstrated high T2 pattern. Consequently, the frequency of the gradient pattern was significantly different between the normal (100%) and pre-arthritic/early-arthritic groups (31%) ($P < 0.0001$). On the femoral ROI, the frequency of the gradient pattern was also significantly different between the normal (93%) and pre-arthritic/early-arthritic groups (50%) ($P < 0.05$).

Comparing the 20 asymptomatic hips and 20 symptomatic hips, frequency of gradient pattern in the acetabular/femoral cartilages was significantly lower in the symptomatic hips (35%/40%) than the asymptomatic hips (75%/90%) ($P < 0.05$). However, there was no significant difference in T2 value between the asymptomatic and symptomatic hips, and there was no significant correlation between WOMAC pain scores and T2 values at the superior ROI of the cartilage.

Discussion

Degeneration of the articular cartilage in osteoarthritis is associated with concomitant changes in the extracellular matrix components that include disruption of collagenous architecture, depletion of proteoglycan, or an increase/decrease in water content, even at very early stages of the disease[30,31]. There is a high expectation, based on numerous experimental and clinical studies, that assessment of T2 of the cartilage will become a potent surrogate of cartilage matrix changes such as these, as well as the associated loss of biomechanical function. Nieminen *et al.* observed an increase of T2 in the superficial zone of bovine cartilage following degradation of collagenous architecture by enzymatic treatment[32]. Lüsse *et al.* demonstrated a close correlation between the water content within the cartilage and T2 relaxation rates for human cartilage removed from the knee joint; the authors stated that the water content could be accurately estimated from the correlation of T2[33]. Wayne *et al.* showed significant inverse correlations of T2 with proteoglycan content or cartilage stiffness, using porcine patella cartilage with depletion of proteoglycan matrix following enzymatic treatment[15]. For *in vivo* imaging of the knee joint, an increase in T2 was associated with aging[17,34] and the involvement of osteoarthritis[18], while a decrease in T2 was associated with the stress of running[35] and also with mechanical loading of the knee during MR imaging[36]. Other than the knee joint, T2 assessment *in vivo* has also been performed for interphalangeal joint cartilage[37]; however, to the best of our knowledge, T2 assessment of the hip joint has yet to be conducted.

Almost all hips of normal volunteers in the present study showed the gradient pattern of T2 mapping at the superior portion of the acetabular and femoral cartilages. This spatial variation, with T2 values increasing from the cartilage base toward the articular surface, is consistent with previous reports of normal knee cartilage T2 values *in vivo*[17,28]. This T2 distribution was accounted for histologically by the physiological spatial distribution of water, collagen and proteoglycan, and by spatial differences in collagenous architecture[17]. High T2 values in the limited distance from the bone/cartilage interface were described in a detailed quantitative analysis of T2 variation of normal knee cartilage[17,28], but were not seen in the hip cartilages of the present study. T2 variations in these earlier studies of the knee were partly explained by chemical shift artifact and volume averaging artifact at the bone/cartilage interface[17,28]. Average T2 values of the acetabular and femoral cartilages in

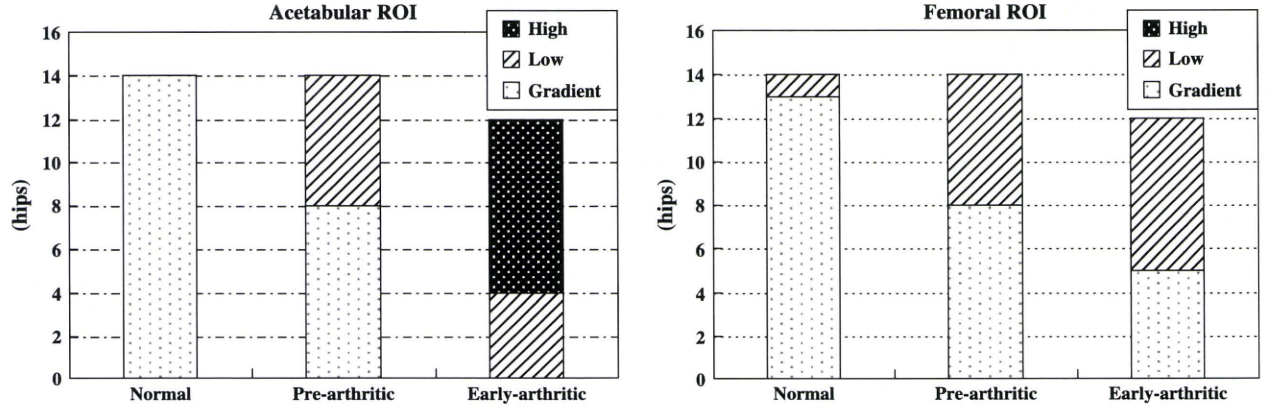

Fig. 3. Distribution of gradient T2 pattern, low T2 pattern and high T2 pattern in the normal, pre-arthritic, and early-arthritic groups, for the acetabular ROIs and femoral ROIs.

the healthy female volunteers (29–33 ms) of the present study were relatively low compared with those observed in the knee cartilages of healthy women of a similar age (40–60 ms) using 3 T MR imaging[34]. A previous cadaveric study revealed that mean cartilage thickness of the hip joint is significantly thinner than the thickness of cartilage in the knee joint, and that thinner cartilage is correlated with a higher compressive stiffness of the cartilage[38]. Considering that compressive stiffness of the cartilage is significantly related to water content or proteoglycan content[39,40], the difference in average T2 values between our study and a previous knee study may partly reflect the physiological differences of those matrix components at the two sites.

The favorable results of the present study might partly result from the superior hardware capability of 3 T MR imaging. MR imaging of the hip cartilage has been difficult at conventional magnetic field strengths ($\leq$1.5 T) because of the relatively thin structure of the acetabular or femoral cartilages, their location deep inside the body, and the close contact between the acetabular and femoral cartilages[41]. MR imaging with high magnetic field strength improves image quality and precision because of the superior signal-to-noise ratio and spatial resolution[19,42–44]. If the cartilage thickness of the hip joints is generally assumed to range from 1 to 3 mm[38,45], the MR images at 3 T in the present study contain approximately 3–10 pixels across each of the acetabular and femoral cartilages. We consider that this high-resolution imaging with high signal-to-noise ratio might be effective in classifying T2 mapping patterns and differentiating between the acetabular and femoral cartilages. However, additional studies to compare diagnostic accuracy and reproducibility between MR images at 3 T and at conventional 1.5 T are necessary to determine true advantages of using 3 T on imaging of hip cartilage.

In contrast to the normal hips of volunteers in the present study, the hips in the early-arthritic groups showed a high frequency of the high T2 pattern in the acetabular cartilage. The tendency of an increase in T2 associated with arthritic involvement agrees with previous results concerning high T2 in patients with knee osteoarthritis[18]. Abnormal elevation of T2 is accounted for pathologically by an increase in water content and water mobility associated with a decrease in proteoglycan content and disruption of the collagen network[18,32]. Predominant occurrence of high T2 pattern in the acetabular cartilage agrees with previous arthroscopic findings[25] showing high frequency of cartilage disorder in the superior acetabular cartilage at early-arthritic stages of hip dysplasia. An interesting finding of the present study is the high frequency of the low T2 pattern in the acetabular and femoral cartilage of the pre- and early-arthritic group. There are several possible explanations for this specific pattern of T2 mapping. First, the cartilage in dysplastic hips is prone to increasing biomechanical stress at the weight-bearing area due to reduced contact area between the opposing surfaces[46]. Previous interventional studies of the knee cartilage showed that axial loading by mechanical loading apparatus and cyclic compressive load by running exercise had a T2-shortening effect, presumably due to the loss of water content or an increase in collagen fiber anisotropy[35,36]. The long-term biomechanical environment of elevated stress distribution in dysplastic hips could lead to a different quantity and distribution of the cartilage matrix compared to normal hips, leading to different mapping of the low T2 pattern. Second, the articular cartilaginous structure of the hip progressively changes during postnatal developmental periods. In dysplastic hips, the inverted or hypertrophic labrum may cover the outer surface of the acetabular articular cartilage after birth and may subsequently constitute a portion of the acetabular cartilage after the childhood developmental periods are completed[47–49]. Because the labrum has a considerably different extracellular matrix structure from the hyaline cartilage, with poor glycoaminoglycan and disorganized collagen fibril[49], acetabular cartilage with a mixture of original labral components might provide a low T2 pattern in T2 mapping. Hip of the early-arthritic group might present with either low T2 or high T2 pattern in the acetabular cartilage, depending on severity of involvement of degenerative changes. Although further follow-up of hips with high and low T2 patterns is needed to determine the clinical relevance of these specific patterns, it is tempting to suggest that T2 assessment may not only provide early detection of osteoarthritic degeneration but also enable the detection of developmental pathological disorders of the cartilage matrix that may lead to disorders of biomechanical function on load-bearing in cases of hip dysplasia.

Quantitative assessment of T2 values within the defined ROI failed to show significant differences among the three groups, although average T2 values of the acetabular ROI for the pre-arthritic group were relatively low and those for the early-arthritic group were relatively high, as compared with the normal group. There is considerable variation in T2 values along the cartilage depth in response to physiological non-uniform distribution of extracellular matrix in normal cartilage[17,28]. Degenerative change of matrix components in the early phase is likely to occur in a superficial or small localized area[17]. Average T2 values of bulk ROI from the cartilage base to the articular surface might be insufficiently sensitive to detect small T2 changes in a regional area, requiring the use of other quantitative methods such as comparison of T2 profile curves as a function of normalized distance from the bone/cartilage interface to the cartilage surface[17,28], or the enhancement of abnormal T2 adjusted by standard T2 value distributions within the cartilage at each pixel.

Pain assessment using the WOMAC score was not correlated with T2 assessment in the hip cartilage at the superior zone. This absence of correlation may partly reflect the relatively mild level of hip pain in the present study. In addition, there are many potential sources of hip pain other than disorders of the articular cartilage, including labral tear, synovitis, ganglionic cyst, and loose body[50]. Previous arthroscopic studies for dysplastic hips at the pre-arthritic stage indicated a high correlation between hip pain and labral tear[51]. The status of labral disorders might have a stronger influence on pain severity than the status of articular cartilage disorders investigated in the present study.

There are several limitations in the present study. First, the pulse sequences available in this study meant that T2 values were calculated from two echoes. In many previous studies, T2 was calculated from more than two echo images and the initial echo image obtained from a multi-echo sequence was excluded in calculating T2 to minimize T2 inaccuracy caused by stimulated echoes[17,28,37]; however, a previous study that used a dual-echo spin-echo sequence for T2 assessment successfully achieved significant differences between the knee cartilages of healthy subjects and those of patients with osteoarthritis[18]. Given the similarities of the gradient pattern of T2 mapping in the present study to previous findings in knee cartilage[17,28], we consider that T2 assessment using a dual-echo spin-echo sequence allowed reliable assessment of the extracellular matrix in the hip cartilage. Second, reliability of T2 assessment was influenced both by reproducibility of acquisition of

MR images and reproducibility of T2 calculation such as definition of ROI or judgment of visual appearance of T2 mapping patterns. Acceptable reproducibility of T2 calculation was obtained in this study with inter-observer reliability ranging from 2.5% to 3.8%. However, reproducibility of acquisition of MR images by scanning repeatedly was not evaluated, and it is unknown how variations in acquisition of MR images influenced the outcomes. Third, this was a feasibility study that conducted comparison of T2 values and mapping patterns between the normal hips and dysplastic hips only at the superior zone, where assessment is particularly important for dysplastic hips, based on biomechanical condition and assessment of osteoarthritis progression. However, additional care should be taken in interpreting T2 values in further studies to assess other anterior or posterior areas of the hip cartilage. Collagen fibril orientation of the cartilage against the static magnetic field differs considerably between the anterior, superior, and posterior regions because of the strongly curved structure of the articular cartilage of the hip. Assessment of T2 values may be significantly influenced by the variations in collagen fibril orientation associated with cartilage positions[52]. Finally, the number of normal volunteers and patients with hip dysplasia was small. The subjects were limited to female gender, and predominantly young subjects were examined both in volunteers and patients, partly due to the low frequency of pre-arthritic or early-arthritic stages in older patients with hip dysplasia. Previous reports showed that T2 in the knee joint was influenced significantly by age[17] and insignificantly by gender[21]; however, it is unknown whether these factors influence the T2 of hip cartilage. Further studies are required to explore the degree of influence of age, gender, and other relevant factors on hip cartilage T2.

In summary, this preliminary study reveals that T2 assessment using 3 T MR imaging shows promise in the early detection of osteoarthritic degeneration and in the detection of developmental pathological disorders of cartilage matrix in patients with hip dysplasia. A combination of T2 assessment and other quantitative assessment techniques such as dGEMRIC[53], which is sensitive to cartilage proteoglycan content, may enable further detailed assessment of fundamental cartilage disorders in patients with dysplastic hips and enhance the early detection of the degeneration of hip cartilage.

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