

Time-Dependent Change in Cartilage Repair Tissue Evaluated by Magnetic Resonance Imaging up to 2 years after Atelocollagen-Assisted Autologous Cartilage Transplantation: Data from the CaTCh Study

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Abstract

Objective. To elucidate the time course of magnetic resonance imaging (MRI)–based morphological and qualitative outcomes after an atelocollagen-assisted autologous chondrocyte implantation (ACI) and to analyze the correlation between arthroscopic and MRI-based assessment. **Design.** We included ACI recipients from a multicenter registration study (CaTCh [Cartilage Treatment in Chiba] study). Morphological (3-dimensional magnetic resonance observation of cartilage repair tissue: 3D-MOCART, MOCART2.0) and qualitative assessment (T2- and T1rho-mapping) by MRI were conducted at 6, 12, and 24 months post-implantation. Global T2 and T1rho indices (T2 and T1rho in repair tissue divided by T2 and T1rho in normal cartilage) were calculated. Arthroscopic second-look assessment was performed in 4 and 15 knees at 12 and 24 months post-implantation, respectively. **Results.** The 3D-MOCART over 12 months witnessed significant patient improvement, but some presented subchondral bone degeneration as early as 6 months. The MOCART2.0 improved from 57.5 to 71.3 between 6 and 24 months ($P = 0.02$). The global T2 index decreased from 1.7 to 1.2 between 6 and 24 months ($P < 0.001$). The global T1rho index decreased from 1.5 to 1.3 between 6 and 24 months ($P = 0.004$). Normal or nearly normal ICRS-CRA (cartilage repair assessment scale developed by the International Cartilage Repair Society) grades were achieved in 86% and 93% of the lesions at 12 and 24 months, respectively. Better ICRS-CRA grade corresponded to better MOCART2.0, with no trend in the T2 and T1rho values. **Conclusions.** Atelocollagen-assisted ACI improved the MRI-based morphological and qualitative outcomes until 24 months post-surgery, and normal or nearly normal grades were achieved in most lesions by arthroscopic assessment. MRI assessment may be an alternative to arthroscopic assessment.

Keywords

autologous chondrocyte implantation, arthroscopic evaluation, MOCART, T2-mapping, T1rho-mapping

Introduction

The hyaline type articular cartilages of joints comprise an extracellular matrix of type II collagen and proteoglycan (PG), chondrocytes, and water that accounts for 70% to 80% of wet weight.¹ It is well known that the articular cartilage has a very low cell density, and lacks blood vessels, nerves, and lymphatic vessels. Thus, due to the poor self-repairing ability, tissue repair mechanisms are unlikely to occur in injury.² Although many attempts have been made

to treat articular cartilage defects, none have successfully replaced large osteochondral defects with long-lasting hyaline cartilage.

Among the currently existing procedures, autologous chondrocyte implantation (ACI) is expected to repair cartilage defects that exceed 4 cm² with good repair tissues approximating the hyaline cartilage.³ Ochi and colleagues developed the third-generation matrix-associated ACI to create a cartilage-like tissue *ex vivo* in a 3-dimensional (3D) culture using atelocollagen gel, from which telopeptides



have been removed to eliminate the antigenic determinants of bovine type I collagen.⁴ This atelocollagen-assisted ACI preserves the phenotype of the cultured chondrocytes and enables even distribution of cells in the transplanted tissue. It also has a lower risk of chondrocytes leakage from the grafted site. They reported that the implanted tissue matured to hyaline-like cartilage at an average of 12 months.⁴ However, other authors reported that the repair tissue remains fibrocartilage-like at 12 months and matures to hyaline-like cartilage at an average of 19.8 months.⁵ It has been reported that the final repair tissue may be fragile immature fibrocartilage in some cases. The process and time course of repair tissue maturation remain to be elucidated.

Currently, there is no established method to reliably evaluate the quality of the repaired tissue after ACI. Determining the condition of the repair tissue after ACI would help evaluate the therapeutic effect and predicting long-term prognosis. The gold standard for analyzing the status of the repair tissue is arthroscopic assessment and biopsy, although it is invasive.

Magnetic resonance imaging (MRI) is a non-invasive method for morphologically evaluating cartilage defects and repair.⁶ Knee protocols with standard 2-dimensional sequences and more advanced isotropic 3D MRI can provide a detailed morphological evaluation.⁷ Moreover, T1rho- and T2-mapping are increasingly being used for biochemical analyses. T1rho relaxation time can evaluate glycosaminoglycan (GAG) concentration and water content of articular cartilage,⁸ whereas T2 relaxation time can evaluate collagen sequence and water content.⁹ Some authors report that the MRI-based outcomes reflect the arthroscopic assessment and can replace more invasive resources such as arthroscopy and biopsy, but this is still debatable.¹⁰⁻¹³

Our current study aimed (1) to elucidate the time course of MRI-based morphological and qualitative outcomes after ACI with atelocollagen gel as a scaffold and (2) to investigate the correlation between arthroscopic assessment and MRI-based outcomes.

Materials and Methods

Study Design

This study was a retrospective analysis of prospectively collected data from a multicenter study registering all ACI

cases in the region (CaTCh study: Cartilage Treatment in Chiba study). The institutional review board of the authors' institution approved the design and publication of this study. The collected data were anonymized for storage and analysis. The MRI and arthroscopic evaluation were performed by an independent evaluator without any information on the patient characteristics and clinical outcomes.

Patient Selection

All patients who received atelocollagen-assisted ACI⁴ at each of the participating facilities of the CaTCh study were registered in a multicenter study. Among these registered patients, those who underwent surgery between February 2016 and April 2018 were candidates for the present study. The inclusion criteria for this study included those who were followed up for at least 2 years; those who completed the scheduled imaging evaluations by MRI—including T2-mapping⁹ and T1rho-mapping⁸ at 6, 12, and 24 months after ACI surgery; and patients without a history of cartilage repair surgery. Patient characteristics including age, sex, body mass index (BMI), diagnosis leading to ACI surgery (traumatic cartilage injury or osteochondritis dissecans), the number of lesions per knee, the total size of cartilage injury per knee, and the location of the lesion were collected from medical records.

Surgical Technique and Postoperative Procedure

All patients underwent a 2-stage atelocollagen-assisted ACI.⁴ In the first surgery, an arthroscopic biopsy was performed to collect 0.4 g of normal cartilage from the non-weightbearing areas of the knee. The cartilage tissue was subjected to enzymatic digestion, the extracellular matrix was removed, and the chondrocytes were isolated.⁴ Chondrocytes were isolated from the cartilage tissue, embedded in an atelocollagen gel (Koken Atelocollagen Implant, Koken Co., Ltd., Tokyo, Japan), and cultured for 4 weeks until the second surgery for implantation. During the second surgery, damaged cartilage tissue was removed from each lesion, and an atelocollagen gel containing immature chondrocytes was implanted. The implanted tissue was covered with an autologous periosteal patch and secured using suture anchors and nylon sutures. The postoperative protocol was not uniform among these patients, because it was mainly dependent on the lesion site, whether it was in the patellofemoral joint or femorotibial joint.

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Table 1. Magnetic Resonance Imaging Protocol.

Orientation	Contrast	Sl. thick, mm	TR, ms	TE, ms	FOV, mm	Flip angle, deg	Pixel bandwidth, Hz/pix	Pixel spacing, mm	Acquisition type
3.0 T									
sag /axi	PD	3	2,550	30	150	90	354	0.55 × 0.55	TSE
cor	PD	3	1,700	30	150	90	546	0.51 × 0.45	TSE FS
cor	PD	0.55	1,200	30	150	90	676	0.55 × 0.55	3D PD TSE
sag	T1rho-map	3	5	3	140	35	718	0.55 × 0.55	GRE
sag	T2-map	3	2,000	10~80	140	90	291	0.48 × 0.48	Multi spin-echo
1.5 T									
sag	PD	3	3,049	15	150	90	313	0.54 × 0.42	TSE
axi	PD	3	3,049	15	150	90	316	0.42 × 0.53	TSE
cor	PD	3	2,000	15	150	90	208	0.63 × 0.63	TSE FS
cor	PD	0.55	1,100	32	151	90	451	0.51 × 0.54	3D PD TSE
sag	T1rho-map	3	5	3	140	35	519	0.55 × 0.55	GRE
sag	T2-map	3	1,500	10~80	140	90	336	0.49 × 0.49	Multi spin-echo

FOV = field of view; sag = sagittal; axi = axial; PD = proton density; TSE = turbo spin echo; cor = coronal; FS = fat saturation; GRE = gradient recalled echo.

MRI Evaluation

The structural and compositional changes of the implanted tissue were evaluated by MRI at 6, 12, and 24 months after implantation surgery. The MR images were acquired using a 1.5 tesla (T) or 3.0 T magnet system (Ingenia, Philips Healthcare, Best, The Netherlands), by placing the patients in a supine position with the knee slightly flexed in the center of a dedicated knee coil. The complete MRI protocol is shown in **Table 1**. The 3D magnetic resonance observation of cartilage repair tissue (MOCART⁷) and MOCART 2.0 knee score¹⁴ were used to quantify the structural changes in the cartilage repair tissue. For compositional evaluation, the repair tissue area was manually registered as the region of interest (ROI) in MATLAB (MathWorks, Natick, MA, USA), version R2020a. The repair tissue was defined on the MRI by identifying the soft anchor inserted in the margin of the lesion to secure the periosteal patch covering the implanted tissue. Then, the MRI slice that represents the largest width of the lesion was selected, and the border of the implanted tissue was traced to define the ROI. The identical slice was selected for follow-up exams, and the ROI was traced to have the same area. Minor adjustment was required in cases of differences caused in image position. To minimize the effect of imaging variations, the measured value was normalized by the value measured in native cartilage. The ROIs for native cartilage were drawn in equal size as the repair tissue, measured at a distance of at least 1 centimeter from the repair tissue to avoid including the damaged cartilage near the repair tissue. The ROIs for the repair tissue and native cartilage were selected to cover the full thickness of the cartilage layer. The evaluation of 3D MOCART, MOCART 2.0, T2-mapping, and T1rho-MR-mapping was performed according to the instructions

published by Welsch *et al.*⁷ and Schreiner *et al.*¹⁴ Repair sites where the T2 or T1rho values could not be measured due to metal artifacts, non-uniform magnetic field, and body movement were excluded. T2 and T1rho indices were calculated with global mean T2 and T1rho values of the repair tissue and global mean T2 and T1rho values of normal, hyaline cartilage, respectively.¹⁵

Arthroscopic Assessment

Arthroscopic evaluation 12 months after implantation was recommended to all patients at the time of informed consent for the initial surgery was taken and was performed in patients who wished for a second-look evaluation by the patient's own will. The implanted tissue was assessed by direct visualization and probing under arthroscopy and graded according to the cartilage repair assessment scale developed by the International Cartilage Repair Society (ICRS): ICRS-CRA.¹⁶ The tissue was assessed for defect filling (by comparing the tissues level with the adjacent normal cartilage), border integrity to adjacent cartilage, and the surface smoothness (by gross appearance). A 12-point scale score was assessed, with up to 4 points awarded each for the degree of repair of the defect, the degree of integration with the surrounding cartilage tissue, and macroscopic appearance. Grade I (12 points) was considered normal, grade II (8-11 points) nearly normal, grade III (4-7 points) abnormal, and grade IV (1-3 points) severely abnormal.

Statistical Analysis

Patient characteristics were presented using descriptive statistics. MOCART 2.0 Knee score, T2, and T1rho index values were analyzed as continuous variables, and the averages

of each time point were compared using a 1-way analysis of variance (ANOVA) with a post hoc Tukey test.

All statistical analyses were conducted using the Bell Curve for Excel (Social Survey Research Information Co., Tokyo, Japan). All tests were 2-sided. Statistical significance was set at $P < 0.05$.

Results

Study Patients

During the study period, a total of 24 knees from 24 patients were registered in the CaTCh study. Among the registered patients, 20 knees from 20 patients, were treated at 4 of the 7 participating institutions and completed the MRI evaluation. A total of 38 cartilage injury lesions were included in the analysis. MOCART assessment was performed in all subjects, while some lesions were not sufficient for T2-mapping or T1rho-mapping assessment due to imaging artifact. T2-mapping measurement was performed on 35 lesions in 19 knees, and T1rho-mapping measurement was performed in 20 lesions in 13 knees. There were 11 males and 9 females, and the mean age at implantation was 45.4 ± 12.4 years old (range, 16-59 years). There were 19 cases of cartilage injury due to trauma and 1 case of osteochondritis dissecans. The mean BMI of all patients was 23.5 ± 3.8 . Ten patients had multiple lesions in one knee, while 10 patients had a single lesion. There were 4, 5, and 1 patients who had 2, 3, and 5 lesions, respectively. The average number of lesions per knee was 2.6 ± 1.1 . Some patients received mosaicplasty for smaller lesions if the patient had multiple lesions. The MRI measurement and arthroscopic assessment were performed only on the ACI-treated sites. Patients had undergone ACI transplantation to the medial femoral condyle ($n = 7$), the lateral femoral condyle ($n = 14$), the medial tibial condyle ($n = 2$), the lateral tibial condyle ($n = 4$), the trochlea ($n = 9$), and the patella ($n = 2$). The mean defect size was $9.3 \pm 4 \text{ cm}^2$ (4-17 cm^2) (Table 2).

Structural Assessment by MRI

The 3D MOCART⁷ and MOCART 2.0 knee score¹⁴ were evaluated at 38 repair sites at 6, 12, and 24 months after implantation. Assessment by 3D MOCART⁷ revealed that the number of lesion sites that showed morphological improvement in the defect fill level, cartilage interface between adjacent normal cartilage, surface and structure, and signal intensity were more. These changes were more apparent 12 months postoperatively. However, some cases presented with degeneration of the subchondral bone—seen as chondral osteophytes, granulation tissue, and cysts—as early as 6 months after ACI, and the cases increased over time (Table 3).

Table 2. Patient Characteristics ($n = 20$).

Age (years) ^a	45.4 ± 12.4
Sex (women/men)	9/11
Diagnosis (trauma/OCD)	19/1
BMI ^a	23.5 ± 3.8
Number of ACI transplantation sites (%)	
1	11 (52%)
2	4 (19%)
3	5 (24%)
5	1 (5%)
ACI transplantation defect size (cm^2) ^a	9.3 ± 4
ACI transplantation sites	
MFC	7
LFC	14
MTP	2
LTP	4
Trochlea	9
Patella	3

OCD = osteochondritis dissecans; BMI = body mass index; ACI = autologous chondrocyte implantation; MFC = medial femoral condyle; LFC = lateral femoral condyle; MTP = medial tibial plateau; LTP = lateral tibial plateau.

^aMean ± standard deviation.

These changes were summarized and quantified using the MOCART 2.0 knee score.¹⁴ The mean MOCART 2.0 score was 57.5 (95% confidence interval [CI], 38.2-76.8), 66.6 (95% CI, 42.8-90.3), and 71.3 (95% CI, 48.7-94) at 6, 12, and 24 months, respectively. The increase between 6 and 24 months was statistically significant ($P = 0.02$) (Fig. 1).

Compositional Quality Assessment by MRI

The quality of the implanted tissue was quantitatively assessed using T2-mapping⁹ and T1rho-mapping.⁸ The T2 values were measured at 35 repair sites at 6, 12, and 24 months after implantation. The mean T2 values of repair tissue decreased from 50 ms at 6-month follow-up to 35.6 and 33.1 ms after 12 and 24 months, respectively. In addition, the global T2 index values decreased from 1.7 at the 6-month follow-up to 1.3 and 1.2 after 12 and 24 months, respectively. The decrease was statistically significant at postoperative months 6 to 12 ($P < 0.001$) (Figs. 2 and 4A). The T1rho values were measured at 20 repair sites at 6, 12, and 24 months after implantation. The number of evaluated sites was lower in the T1rho evaluation because of its susceptibility to imaging artifacts. The T1rho values decreased from 70.4 ms at 6-month follow-up to 63.2 and 57.2 ms after 12 and 24 months, respectively. Moreover, the global T1rho index values decreased from 1.5 at 6-month follow-up to 1.4 and 1.3 after 12 and 24 months, respectively. The decrease in T1rho index values was statistically significant

Table 3. The 3D-MOCART.

Variables	Class	Number of lesion sites			
		6 mo	12 mo	24 mo	
1. Defect fill	0%	1	1	1	
	0%-25%	10	7	4	
	25%-50%	4	5	4	
	50%-75%	8	4	4	
	75%-100%	8	7	4	
	100%	3	4	10	
	100%-125%	2	2	4	
	125%-150%	0	3	2	
	150%-200%	1	3	3	
	>200%	1	2	2	
2. Cartilage interface	Sagittal	Complete	17	21	22
		Demarcating border visible (split-like)	9	6	7
		Defect visible <50%	7	8	6
		Defect visible >50%	5	3	3
	Coronal/axial	Complete	16	21	25
		Demarcating border visible (split-like)	10	6	5
3. Bone interface		Defect visible <50%	7	8	5
		Defect visible >50%	5	3	3
		Complete	25	25	25
		Partial delamination	12	10	10
4. Surface		Complete delamination	1	3	3
		Delamination of periosteal flap	0	0	0
		Surface intact	4	12	19
		Surface damaged <50% of depth	15	14	11
5. Structure		Surface damaged >50% of depth	19	12	8
		Adhesions	0	0	0
		Homogeneous	7	18	20
		Inhomogeneous of cleft formation	31	20	18
6. Signal intensity		Normal	9	20	23
		Nearly normal	16	11	5
		Abnormal	13	7	10
7. Subchondral lamina		Intact	17	20	28
		Not intact	21	18	10
8. Chondral osteophytes		Absent	35	32	26
		Osteophytes <50% of the thickness of the cartilage transplant	2	3	9
		Osteophytes >50% of the thickness of the cartilage transplant	1	3	3
9. Bone marrow edema		Absent	27	31	32
		Small (<1 cm)	7	3	5
		Medium (<2 cm)	2	3	0
		Large (<4 cm)	2	1	1
		Diffuse	0	0	0
10. Subchondral bone		Intact	23	17	13
		Granulation tissue	10	13	15
		Cyst	5	8	10
		Sclerosis	0	0	0
11. Effusion		Absent	6	11	26
		Small	11	19	10
		Medium	21	8	2
		Large	0	0	0

Overview of the 3D-MOCART results in a postoperative course of 24 months.
MOCART = magnetic resonance observation of cartilage repair tissue.

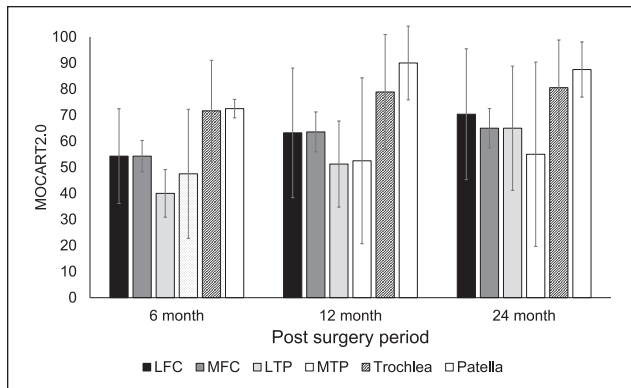


Figure 1. Postoperative change of the MOCART 2.0 score in each lesion site. MOCART = magnetic resonance observation of cartilage repair tissue; LFC = lateral femoral condyle; MFC = medial femoral condyle; LTP = lateral tibial plateau; MTP = medial tibial plateau.

between 6 and 24 months after implantation ($P = 0.004$) (Figs. 3 and 4B).

Arthroscopic Assessment

Arthroscopic second-look assessment was performed on 7 repair sites in 4 knees at 12 months and on 30 repair sites in 15 knees at 24 months after implantation. Normal or nearly normal ICRS-CRA grades (ICRS-CRA grade 1 or 2) were achieved in 86% of the lesions at 12 months and 93% at 24 months after implantation (Fig. 5).

We compared the mean total MOCART 2.0 score in each ICRS-CRA grade in Fig. 6A to analyze if the MRI structural evaluation will have similar result with the arthroscopic assessment. The MOCART 2.0 score consists of 7 variables: (1) volume, (2) integration (3) surface, (4) structure, (5) signal intensity, (6) bony defect/overgrowth, and (7) subchondral changes, of which the latter 4 variables could not be evaluated by arthroscopic assessment. Therefore, we compared the sum of the 3 variables—volume, integration, and surface—that could be assessed by arthroscopy with ICRS-CRA grading in Fig. 6B. There was only one ICRS-CRA grade 3 subject and only 2 ICRS-CRA grade 4 subjects. There was a trend of higher (better) total MOCART2.0 and the subtotal of its 3 variables (defect filling, integration, and surface) corresponding to lower (better) ICRS-CRA grade. On the contrary, there were no clear trend in global T2 and T1rho indices against each group of ICRS scores (Fig. 7A and B).

Discussion

In the present study, structural and compositional MRI assessment as well as arthroscopic assessment revealed that the repair tissue improved morphologically and qualitatively over time up to 24 months after atelocollagen-assisted ACI.

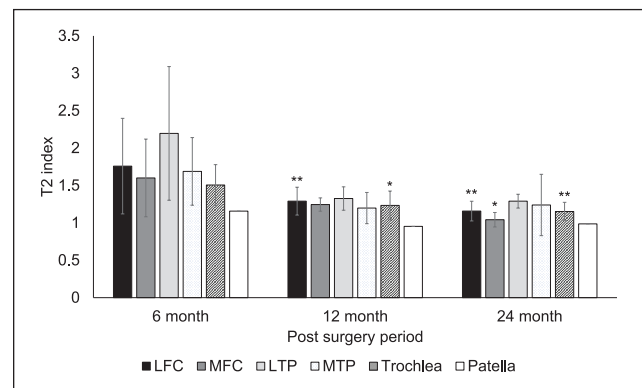


Figure 2. Postoperative change of the mean T2 values in each lesion site. LFC = lateral femoral condyle; MFC = medial femoral condyle; LTP = lateral tibial plateau; MTP = medial tibial plateau. ** $P < 0.01$ compared with values at 6 months. * $P < 0.05$ compared with values at 6 months.

The arthroscopic assessment indicated that 93% at 24 months after implantation had good or excellent outcomes. Furthermore, the results from comparison of MRI evaluation and arthroscopic scoring, indicating a trend of better MOCART2.0 corresponding to better ICRS-CRA grading while T2-mapping and T1rho-mapping values not matching ICRS-CRA-grades, suggest that MRI may allow similar evaluation of the structural improvement, while the arthroscopic evaluation does not reflect the qualitative changes.

Quantitative Analysis

Previous studies have shown that the MOCART scores improved 12 months after atelocollagen-assisted ACI, and this continued until the final follow-up.^{17,18} Other third-generation ACI studies that included radiological results after 2 years showed the MOCART score was all graded as good. In addition, Zak *et al.*,¹⁹ who used an Igor scaffold, showed that the MOCART 2.0 knee score was 78 at 24 months after implantation. Similar to previous reports, our current study showed that the MOCART 2.0 knee score significantly improved from 57.5 at 6 months after implantation to 71 at 24 months.

By 3D MOCART assessment, the number of cases that presented morphological improvement of the cartilage repair tissue increased over time, and the improvement was confirmed from 12 months after implantation. Conversely, as early as 6 months after implantation, some cases present with degeneration of subchondral bone seen as chondral osteophytes, granulation tissue, and cysts. In these cases, MOCART2.0 decreased with decreasing defect fill and increasing subchondral changes. Adachi *et al.* and Takazawa *et al.* reported that a slight subchondral change was seen beneath the implanted site at 6 years, but the MOCART score did not decrease. Moreover, Zak *et al.* reported that

the defect fill of the repair tissue decreased, and the appearance of subchondral bone changes increased between 12 and 24 months in some cases. Therefore, MOCART 2.0 decreased from 5 to 10 points between 12 and 24 months.¹⁹

Previous studies showed a 3-fold increase in the failure rate of ACI after previous marrow stimulation such as microfracture.^{20,21} In addition, the preoperative subchondral bone injury was significantly associated with post-ACI subchondral bone changes.²² The subchondral changes observed in our cases may be degeneration that occurs in the early phase after surgery, possibly suggesting damage to

the subchondral bone before ACI surgery. Another possibility may be that the surgical procedure, such as anchor insertion, caused damage to the subchondral bone, which progressed over time.

Qualitative Analysis

As arthroscopy is invasive and unsuitable for repeated longitudinal follow-up, MRI has become the preferred method for non-invasive follow-up of patients after cartilage resurfacing procedures. dGEMRIC imaging requires injection of gadolinium contrast and thus is more invasive and places greater demands on the imaging center and patient.²³ Conversely, T1rho- and T2-mapping can probe the macromolecular structure of articular cartilage through different mechanisms in a completely non-invasive manner indistinguishable from traditional qualitative MRI. Ultrastructural alterations to collagen and PGs can be detected by changes in T1rho and T2 values. By using spin-lock techniques, T1rho is believed to be more sensitive to PG content,^{24,25} while T2, through its analysis of free water proton molecule motion within the cartilaginous matrix, is believed to be highly sensitive to the orientation, concentration, and integrity of collagen in the articular cartilage.^{9,26-28}

Quantitative T2- and T1rho-mapping for the assessment of cartilage repair comprises intact articular cartilage as a direct gold standard within the same joint. Therefore, we described the individual relative T2 and T1rho values with a T2 and T1rho index. This is because we considered the

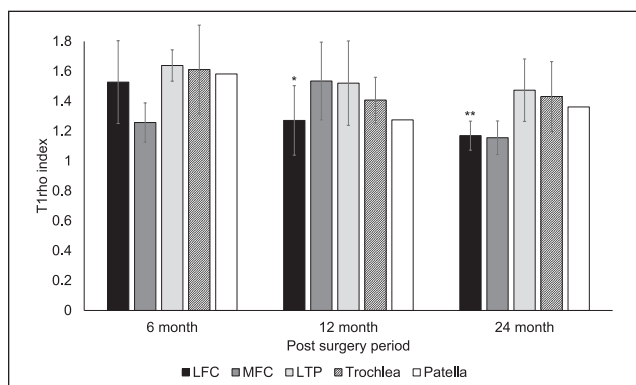


Figure 3. Postoperative change of the mean T1rho values in each lesion site. LFC = lateral femoral condyle; MFC = medial femoral condyle; LTP = lateral tibial plateau; MTP = medial tibial plateau. ** $P < 0.01$ compared with values at 6 months. * $P < 0.05$ compared with values at 6 months.

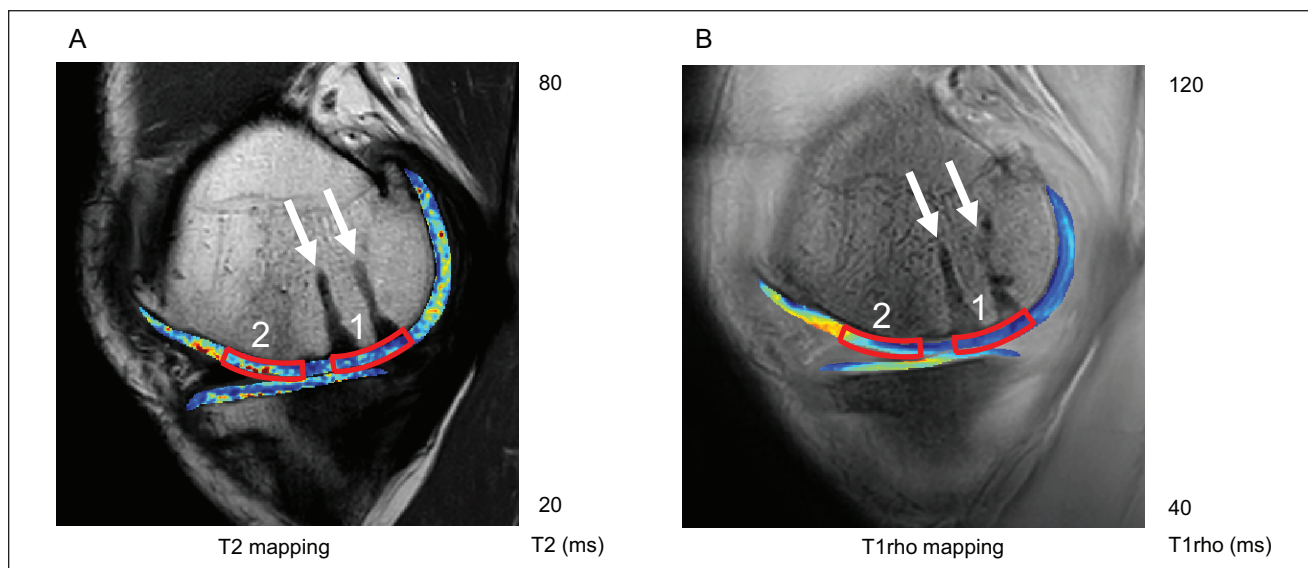


Figure 4. T2- and T1rho-mapping of a 41-year-old male patient 24 months after autologous chondrocyte implantation of the medial femoral condyle. (A) T2-mapping. (B) T1rho-mapping. Color-coded T2-and T1rho-map with analyzed regions of interest: 1 = repair tissue; 2 = native cartilage. Color bars show the scale of T2 and T1rho times in milliseconds. Drilled holes for soft anchors are marked with arrows.

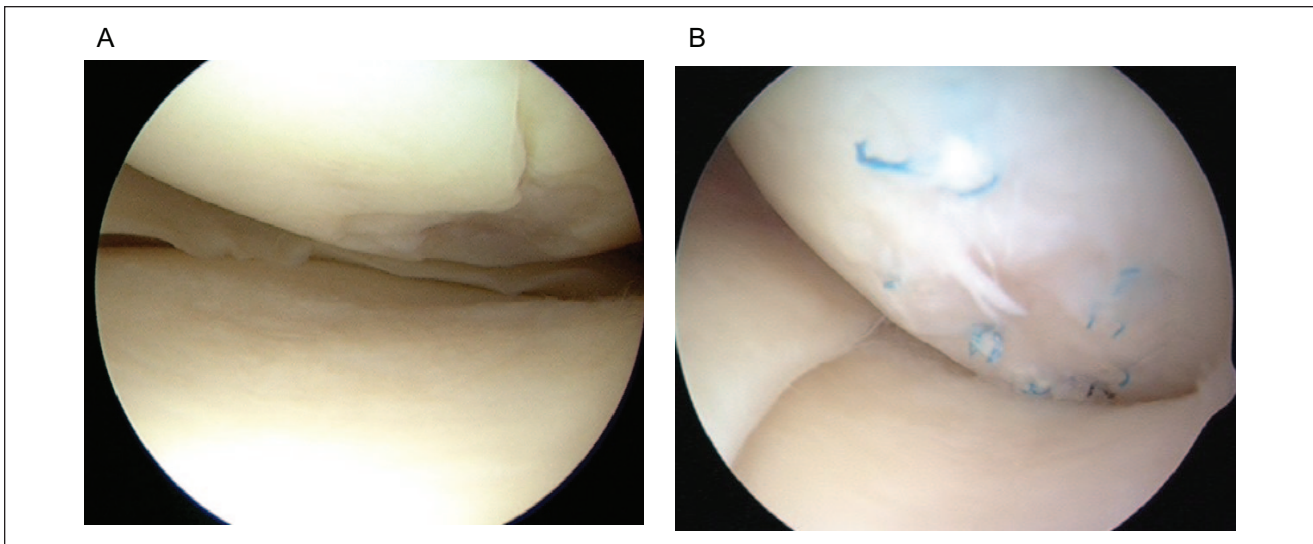


Figure 5. Pre- and postoperative arthroscopic image of a 31-year-old male patient. **(A)** A cartilage defect in the lateral femoral condyle before transplantation. **(B)** Two years after transplantation. The defect is almost fully filled with complete integration to adjacent cartilage and minor fibrillation on the surface, representing a nearly normal (cartilage repair assessment scale developed by the International Cartilage Repair Society grade II) repair.

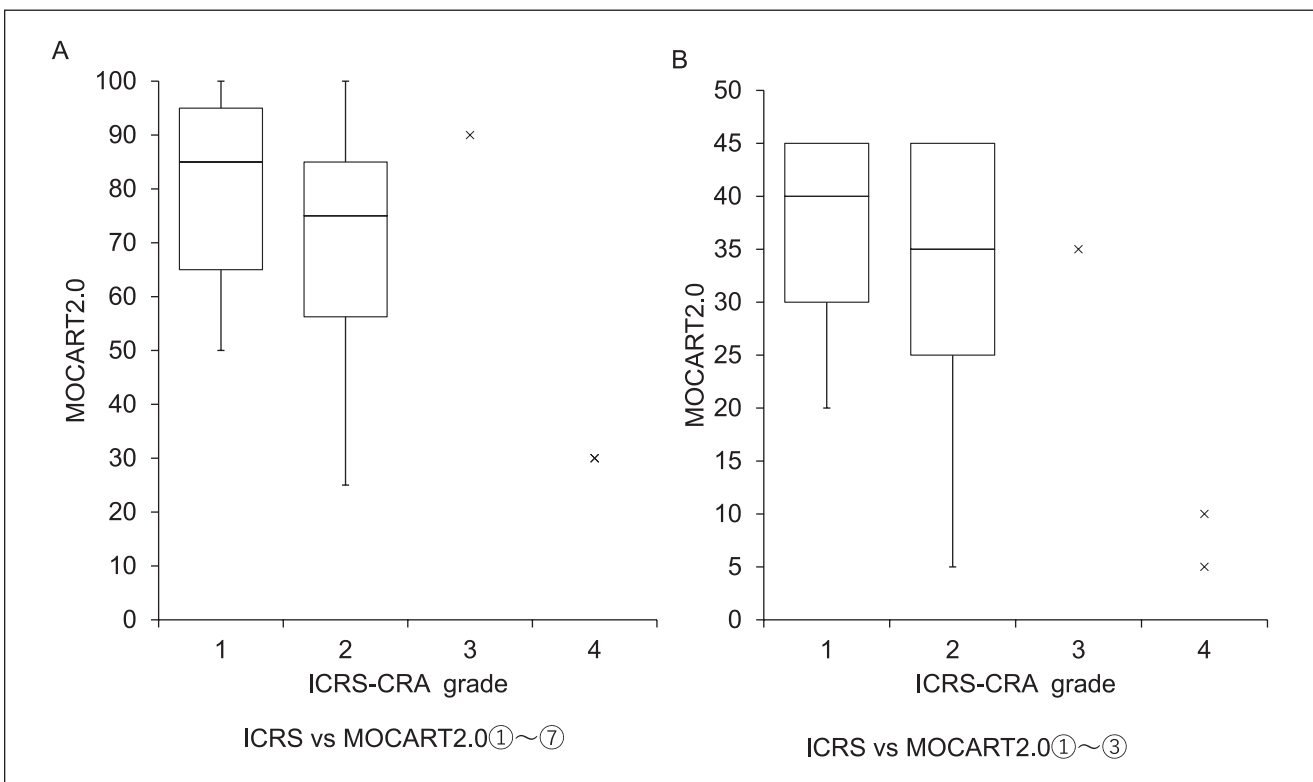


Figure 6. MOCART 2.0 scores in each ICRS-CRA grade. **(A)** Total MOCART 2.0 score and ICRS-CRA grade. There was 1 patient in ICRS-CRA grade 3 whose score was 90. There were 2 patients in ICRS-CRA grade 4 whose score was both 30. The patients were indicated by an X. **(B)** MOCART 2.0 score for 3 variables (defect filling, integration, surface) and ICRS-CRA grade. There was 1 patient in ICRS-CRA grade 3 whose score was 35. There were 2 patients in ICRS-CRA grade 4 whose score was 5 and 10. The patients were indicated by an X. MOCART = magnetic resonance observation of cartilage repair tissue; ICRS-CRA = cartilage repair assessment scale developed by the International Cartilage Repair Society.

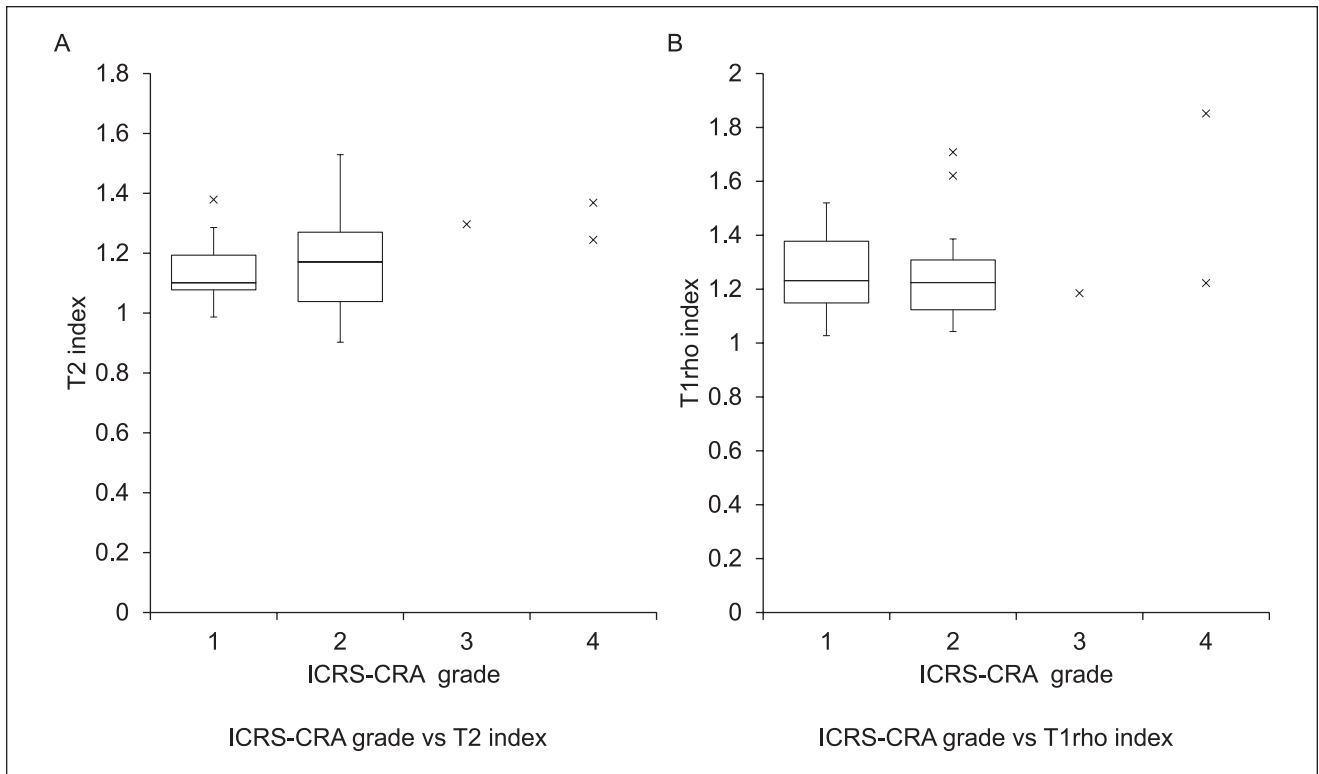


Figure 7. Global T2 and T1rho index in each ICRS-CRA grade. **(A)** Global T2 index and ICRS-CRA grade. There was 1 patient in ICRS-CRA grade 1 whose T2 index was 1.4. There was 1 patient in ICRS-CRA grade 3 whose T2 index was 1.3. Furthermore, there were 2 patients in ICRS-CRA grade 4 whose T2 index was 1.2 and 1.4. The patients were indicated by an X. **(B)** Global T1rho index and ICRS-CRA grade. There were 2 patients in ICRS-CRA grade 2 whose T1rho index was 1.6 and 1.7. There was 1 patient in ICRS-CRA grade 3 whose T1rho index was 1.2. Furthermore, there were 2 patients in ICRS-CRA grade 4 whose T1rho index was 1.2 and 1.9. The patients were indicated by an X. ICRS-CRA = cartilage repair assessment scale developed by the International Cartilage Repair Society.

inter-individual variability of T2 and T1rho values and the difference in the MRI protocol.²⁹

It has been reported that T2 values are similar to those of normal hyaline cartilage at 1 to 3 years.^{15,30,31} However, these studies were cross-sectional and did not explain the time course of cartilage maturation. In our current longitudinal evaluation, the T2 index improved with time to a similar range of normal cartilage tissue by 1 year after implantation.

However, to our knowledge, no study has evaluated the radiographic properties of repair tissue following ACI using T1rho-mapping. In our current study, the T1rho index improved and attained the same value as that of normal tissue by 2 years after implantation. Together with the findings of T2-mapping, it is suggested that the water content and collagen sequence improve in 1 year, but the PG content improvement will take more time.

It has been reported that T1rho-mapping complements T2-mapping in the assessment of repair tissue maturation in Microfracture or Mosaicplasty.^{32,33} No study has examined T1rho and compared the efficacy of T1rho and T2

quantitative MRI in evaluating cartilage regeneration after ACI. We consider T1rho-mapping and T2-mapping to be viable methods to monitor repair tissue maturation overtime after ACI quantitatively and non-invasively. However, the number of patients is low, and there is need for further confirmation of the present study.

MRI-Based Outcomes and Arthroscopic Assessment

Ochi *et al.*⁴ reported that 93% had normal or nearly normal outcomes (ICRS grade 1 or 2) at 24 months after atelocollagen-assisted ACI. In addition, the arthroscopic assessment showed that 92% of the cases were evaluated as normal or nearly normal 12 months after implantation.³⁴ A more recent study reported that arthroscopic findings at 24 months after implantation were graded as normal or nearly normal according to the ICRS scale in 64 of 73 knees (87.7%).¹⁸ In other types of ACI, it was reported that good or excellent outcomes were obtained in 80% of patients at 1 to 1.5 years after implantation³⁵ and a significant correlation was observed

between the ICRS and overall MRI score, especially in defect filling and cartilage signal.³⁶ However, some studies reported no significant correlation between arthroscopic assessment and the MOCART score.¹² The rate of good or excellent outcomes (ICRS grade 1 or 2) was 86% at 24 months after implantation in our study, and lower ICRS grade had a higher total MOCART2.0 score as well as the 3 variables (defect filling, integration, and surface) of the MOCART2.0. The MRI structural evaluation had similar results with ICRS-CRA grading. However, the results of MRI qualitative evaluation (mean global T2 index and mean global T1rho index) did not correspond to ICRS-CRA grades. This suggests that MRI can evaluate the improvement in structural appearance similarly to the arthroscopic evaluation, and MRI has advantage in that it could also assess the quality of the repaired tissue in a non-invasive manner. MRI assessment may be used as an alternative to arthroscopic assessment in terms of morphological evaluation and would provide additional value in the assessment of the quality of repaired tissue, thus being more useful in the postoperative longitudinal monitoring of cartilage repair surgeries.

Comparison with Other ACI

The measured T2 values of repair tissue in our study were lower than those in previous studies.³⁷⁻⁴² The difference may be due to the different types of scaffolds used in each study because the ultrastructure of repair tissue after ACI surgery differs depending on the scaffold. The differentiation status of chondrocytes in the scaffold affects the production of type II collagen and may alter the T2 value of the repair tissue.³⁹ Gavénis *et al.*⁴³ showed a significantly higher type II collagen gene expression and a lower type I collagen gene expression in their collagen gels compared with other matrix systems. Our lower T2 values suggest that atelocollagen-assisted ACI may be favorable for tissue maturation after ACI.

The most common problems after the ACI procedure performed using a periosteal membrane include early delamination, incomplete periosteal graft incorporation into host cartilage, and late hypertrophic periosteal response. Periosteal hypertrophy has been reported in 28% of all patients.⁴⁴ In our series, 5 cases showed graft hypertrophy until 24 months, and 1 case presented with catching that required arthroscopic shaving. Steinwachs reported that the use of an artificial collagen I/III membrane in the fixation of cells during the implantation process could reduce the incidence of symptomatic hypertrophy with the need for revision surgery 36 months after surgery.⁴⁵

This study had several limitations. First, we did not evaluate the preoperative MRI because the images were not obtained in the same manner, and there were considerable variations in the image quality. Therefore, we were unable to distinguish the changes observed 6 months after surgery from those occurring before ACI surgery. In some cases, subchondral changes, such

as cysts or cartilaginous osteophytes, might have been observed before ACI. Second, the patients were not homogeneous, with variability in the number and location of lesion sites. Third, although all lesions included were diagnosed as traumatic chondral lesion by the definition of having a clear border from the surrounding normal appearance cartilage tissue, there is possibility that the normal appearing cartilage had potential degeneration and thus affected the measurement. Furthermore, some patients had undergone concomitant surgery, such as anterior cruciate ligament reconstruction, meniscus repair, and limb alignment correction. These variabilities in preoperative comorbidities or concomitant surgeries might have influenced the tissue maturation process. Ideally, a study on patients with single lesions in the same compartment without any combined injuries would more easily evaluate tissue maturation in a uniform environment.

However, it is common that some combined injuries occur along with cartilage injury and that these procedures are required at the time of cartilage repair.⁴⁶ Therefore, our results could be expected to reflect the tissue maturation process observed in daily practice. Finally, we were unable to determine the actual pathology of the changes in T1rho and T2 values. The only way to definitively assess the underlying pathology is to perform a biopsy for histological assessment. However, as previous studies have reported better histological maturation with lower T1rho and T2 values,⁴⁷⁻⁴⁹ we did not perform this considerably invasive procedure owing to ethical considerations.

In conclusion, the cartilage repair tissue improved morphologically and qualitatively over time up to 24 months after implantation. The arthroscopic assessment showed good or excellent outcomes 12 to 24 months after the implantation, and there was a significant correlation with MOCART 2.0, but no correlation with the T2 and T1rho index between each group of ICRS scores.

Authors' Note

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Declaration of Conflicting Interests

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Ethical Approval

The institutional review board of Chiba university approved the design and publication of this study.

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