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Juvenile Particulate Osteochondral Allograft for Treatment of Osteochondral Lesions of the Talus: Detection of Altered Repair Tissue Biochemical Composition Using 7 Tesla MRI and T2 Mapping

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ABSTRACT

During the previous 2 decades, numerous surgical procedures have become available to treat osteochondral lesions of the talus. The objective of the present study was to use 7 Tesla (7T) magnetic resonance imaging (MRI) to quantify and compare T2 values (a marker of collagen architecture) of native tibiotalar cartilage and cartilage repair tissue in patients treated with a juvenile particulate allograft for osteochondral lesions of the talus. The institutional review board approved the present study, and all subjects provided written informed consent. We scanned the ankles of 7 cartilage repair patients using a 7T MRI scanner with a multi-echo spin-echo sequence to measure the cartilage T2 values. We assessed the cartilage T2 values in the talar repair tissue, adjacent native talar cartilage, and overlying tibial cartilage. We compared the differences between groups using the paired *t* test. The talar cartilage repair tissue demonstrated greater mean T2 relaxation times compared with the native adjacent talar cartilage (64.88 ± 12.23 ms versus 49.56 ± 7.82 ms; $p = .043$). The tibial cartilage regions overlying these talar cartilage regions demonstrated a trend toward greater T2 relaxation times (77.00 ± 31.29 ms versus 59.52 ± 7.89 ms; $p = .067$). 7T MRI can detect differences in T2 values in cartilage repair tissue compared with native cartilage and could be useful for monitoring the status of cartilage health after surgical intervention.

Osteochondral lesions of the talus occur in the setting of ankle trauma or instability (1) and are characterized by a defect of the articular cartilage and the adjacent subchondral bone (2). The challenge of treating lesions of the avascular cartilage was first appreciated in 1743 by Dr. Hunter, who stated that an articular cartilage lesion is a "troublesome thing and once destroyed, it is not repaired" (3). A high failure rate is seen with nonoperative treatment, with <45% of lesions responding favorably (4). Because of the high load per unit area of the tibiotalar joint (5), these patients are at a significant risk of developing debilitating osteoarthritis (5). To relieve symptoms, restore mobility, and prevent long-term arthritic sequelae, various operative treatment options have been developed, including microfracture/drilling, autologous osteochondral transplantation, osteochondral allograft transplantation, and autologous chondrocyte transplantation. No technique appears to be superior to the others (6), and each option has associated strengths and weaknesses (6). Currently, surgeon preference has a significant role in decision making.

Recently, a juvenile articular cartilage graft (DeNovo® NT Graft, Zimmer, Warsaw, IN) (7,8) has been proposed for the treatment of talar osteochondral lesions of the talus <5 cm^2 for patients in whom microfracture chondroplasty failed (9). The DeNovo® NT Graft (Zimmer) is a particulate juvenile articular cartilage obtained from juvenile allograft donors ≤13 years old but typically <2 years old (9). Because of preparation from immature articular cartilage, the DeNovo® NT Graft has a much greater cellular density, cell proliferation rate, cell outgrowth, and glycosaminoglycan content than mature articular cartilage (10). First tested in rabbit models in 1983 (11) and initially

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applied in the clinical context of knee osteochondral lesions (8,12,13), the DeNovo® NT Graft is a 1-stage procedure and thus is an attractive alternative to 2-stage procedures such as autologous chondrocyte transplantation (9). Also, the cost ($3800) is well below that of a matched, fresh talar allograft ($8000 to $10,000) or a second-stage surgical procedure (9). The potential drawbacks of this technique include joint effusion and inflammation, failure of graft incorporation, graft delamination or hypertrophy, and the rare possibility of graft-mediated disease transmission (14–16).

Magnetic resonance imaging (MRI) provides the best method to visualize and assess talar lesions, including the ability to accurately quantify the dimensions of the cartilage defect (17). The use of MRI to study articular cartilage lesions of the talus has been demonstrated in several studies. Using 3 Tesla (3T) MRI, Gatlin et al (18) demonstrated the diagnostic accuracy for detecting Outerbridge grade 3 and 4 lesions: sensitivity of 0.714, specificity 0.738, positive predictive value 0.370, and negative predictive value of 0.923 with respect to the reference standard arthroscopy (18). More recently, advanced biochemical MRI methods, which have the potential to assess cartilage molecular composition, have been successfully applied at both high-field (3T) (19) and ultra-high-field (7T) (20,21) in patients who have been treated with microfracture and matrix-associated autologous cartilage transplantation. The advantage of performing MRI at 7T is the higher signal-to-noise ratio, which scales approximately linearly with the strength of the main magnetic field.

T2 mapping of the ankle at 7T has the potential to assess the collagen fibril network organization of the native hyaline cartilage and the repair tissue (22). The use of 7T MRI to assess the surgical outcomes in patients who have undergone juvenile particulate cartilage allograft for talar lesions has not been previously reported. In the present study, cartilage T2 values were quantified using 7T MRI in patients who had undergone DeNovo® allograft treatment for talar osteochondral lesions. Specifically, we hypothesized that talar cartilage repair tissue would demonstrate different T2 values compared with native adjacent talar cartilage. This would imply metabolic activity on a molecular level that was previously not quantifiable. Additionally, we hypothesized that the tibial cartilage overlying the talar cartilage repair tissue would also demonstrate altered T2 values compared with adjacent native tibial cartilage.

Patients and Methods

Patient Series

The institutional review board approved the present study, and all subjects provided written informed consent. From the orthopedic foot and ankle division at our institution, we recruited 7 patients. All patients were adults with talar osteochondral lesions in whom conservative treatment and microfracture had previously failed and who were subsequently treated with a juvenile particulate cartilage graft. We excluded patients with other concomitant pathologic features such as malalignment, neoplasm, and inflammatory conditions. Additional exclusion criteria were talar osteochondral procedures that did not use the DeNovo® particulate allograft and patients who had simultaneously undergone concomitant procedures such as osteotomy, ligamentous or tendon repair, or fracture fixation.

Image Acquisition and Generation of T2 Maps

We scanned the surgically treated ankle of all patients using a 7T whole body MRI scanner (Siemens AG, Erlangen, Germany) using a 28-channel lower extremity coil (Quality Electrodynamics, Mayfield Village, OH). We scanned the subjects using a multi-echo spin-echo sequence (repetition time/excitation time [TE] 3000 ms/15, 30, 45, 60, 75, and 90 ms; field of view 0.586 × 0.586 × 2 mm, acquisition time 6 minutes, 29 seconds). Color cartilage T2 maps were generated using in-house–developed software (FireVoxel, New York, NY) using the equation $\ln((S(TE))/S_0 = (-TE/T2)$, where S(TE) is the signal intensity for a given TE, S_0 is the signal at the shortest TE, and C is the intercept. We used a weighted linear least squares fit for the monoexponential decay equation (23).

Image Segmentation

Under the guidance of a musculoskeletal radiologist, the following regions of interests were manually segmented: talar lesion (area corresponding to the osteochondral talar lesion/repair tissue site), talar normal (area corresponding to a normal talar region adjacent to the talar lesion), tibial lesion (overlying tibial cartilage region that articulates with the talar lesion as described), and tibial normal (overlying tibial cartilage articulating with the native cartilage adjacent to the talar lesion/repair tissue).

Statistical Analysis

We used paired *t* tests (SPSS IBM, version 20.0; IBM, Armonk, New York) to compare the average T2 relaxation times between *(1)* talar lesions and native adjacent talar cartilage; and *(2)* tibial lesions and normal tibial cartilage. A p value $<.05$ was considered statistically significant.

Results

Seven patients (mean age 46.9 ± 10.8 years, 4 females, 3 males, 5 left sided, and 2 right sided) were included, with a mean lesion size of 118.4 ± 61.1 mm^2. Four patients had posteromedial lesions, and 1 patient each had a lesion at the following locations: central–anterior, anteromedial, and central–medial (Table 1). Representative 7T images of tibiotalar cartilage from subjects 3 and 6 are shown in Figs. 1 and 2, respectively. The T2 relaxation times for each subject with respect to the talus are listed in Table 2, and the relaxation times for the tibia are listed in Table 3. The mean T2 relaxation times were greater for the talus lesion than for the normal region of the talar cartilage (64.88 ± 12.23 ms versus 49.56 ± 7.82 ms; $p = .043$). A trend was seen toward greater values for the tibial corresponding region compared with the normal tibial cartilage (77.00 ± 31.29 ms versus 59.52 ± 7.89 ms; $p = .067$).

Discussion

We have demonstrated the feasibility of using 7T MRI to detect differences in T2 values and, therefore, the collagen content in ankle cartilage repair tissue in patients who had received a juvenile particulate osteochondral allograft compared with the adjacent native cartilage. A limited number of studies have reported the outcomes of patients with talar lesions treated with a juvenile cartilage allograft (24). Coetzee et al (14) reported the 1-year postoperative outcomes of

Table 1
Patient demographic information

Pt. No.	Age (yr)	Gender	Surgery Side	Lesion Size (mm^2)	Location	Interval From Surgery to MRI (mo)	Comorbidities
1	60	Male	Left	49	Central–anterior	7	Skin cancer at neck region
2	35	Female	Left	99	Posteromedial	12	Appendicitis after appendectomy
3	60	Male	Left	100	Posteromedial	12	None
4	40	Female	Right	240	Anteromedial	32	Vitamin B deficiency, anxiety
5	38	Male	Left	91	Posteromedial	21	None
6	54	Female	Right	100	Central–medial	13	None
7	41	Female	Left	150	Posteromedial	7	Asthma, diabetes
Mean ± SD	46.9 ± 10.8	NA	NA	118.4 ± 61.1	NA	14.9 ± 8.9	NA

Abbreviations: MRI, magnetic resonance imaging; NA, not applicable; Pt. No., patient number; SD, standard deviation.

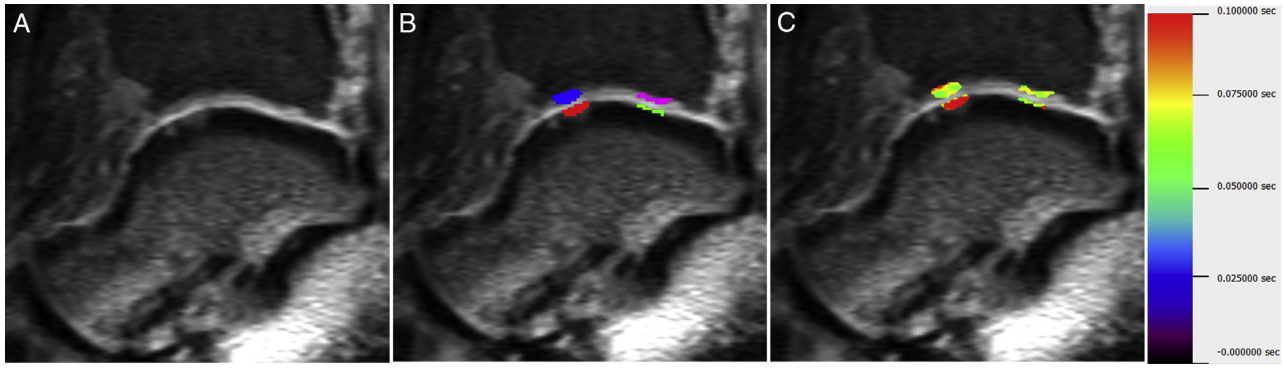

Fig. 1. (*A*) Representative lateral ankle magnetic resonance image at 7 Tesla demonstrating talar osteochondral lesion of subject 3; (*B*) segmented talar osteochondral lesion *(red)*, normal talar region *(green)*, corresponding tibial lesion *(blue)*, and normal tibial region *(purple)*; and (*C*) the corresponding T2 relaxation color map.

24 talar lesions >10 mm treated with particulate juvenile cartilage. Of the patients, 78% demonstrated good to excellent American Orthopaedic Foot and Ankle Society scale scores; 92% of the subjects with moderate-size lesions (10 to 15 mm) demonstrated good to excellent results and 56% of those with large-size lesions (>15 mm), good to excellent results (14). In another study, Bleazey and Brigido (1) reported the 6-month postoperative outcomes of 7 patients treated with cylindrical sponge allograft and particulate juvenile cartilage graft. All patients demonstrated clinically significant improvements in pain and activity scale scores, and postoperative 1T MRI demonstrated the process of subchondral bone incorporation and formation of articular surface. The investigators noted that based on their 6-month follow-up data, this process was visualized as incomplete (1). Adams et al (25) reported their experience with arthroscopically guided juvenile cartilage transplantation and concluded that juvenile particulate cartilage can be successfully used to treat talar lesions using arthroscopic techniques.

A critical need exists to objectively assess cartilage repair tissue quality, which could serve as a biomarker for monitoring and predicting surgical and clinical outcomes in longitudinal studies (26). The present study found that the T2 relaxation times were greater for talar osteochondral lesions treated with a particulate juvenile allograft than for native adjacent talar cartilage. T2 values are a biomarker of cartilage collagen architecture (22); thus, T2 mapping was included in the MRI protocol for the Osteoarthritis Initiative, the National Institutes of Health-funded multicenter, nationwide, longitudinal study of knee osteoarthritis (27). Greater T2 values correspond to altered collagen architecture. In patients with degenerative osteoarthritis, this is believed to reflect the early stages of collagen fiber disorganization with corresponding altered cartilage water content (22,28–30). In patients who have received a juvenile osteochondral allograft, the altered T2 values might reflect a particular stage of cartilage tissue repair. Presumably, if the chondrocytes in the repair tissue are viable, they will be producing collagen in the extracellular matrix. Thus, depending on the stage of the repair tissue or time since surgery, the maturity of the extracellular matrix could vary. Longitudinal studies are necessary in the future to confirm that the T2 values change according to the time after surgery and potentially normalize to that of native adjacent cartilage.

We additionally evaluated whether the tibial cartilage overlying talar cartilage lesions or repair sites demonstrated altered cartilage T2 values compared with native adjacent tibial cartilage. The rationale was that if talar cartilage lesions have decreased shock absorption abilities, abnormal or increased forces would be transmitted to the corresponding articular surface at the tibia, potentially resulting in early tibial cartilage degeneration. This would be similar to the "kissing" or reciprocal osteochondral injuries frequently seen in the lateral femoral condyle and lateral tibial plateau in the setting of anterior cruciate ligament injury. Our results showed that only a trend ($p = .067$) was seen toward greater T2 relaxation times for the tibial cartilage overlying talar cartilage lesions compared with the native adjacent tibial cartilage. It is likely that more subjects would be necessary to achieve sufficient statistical power to detect differences between the groups.

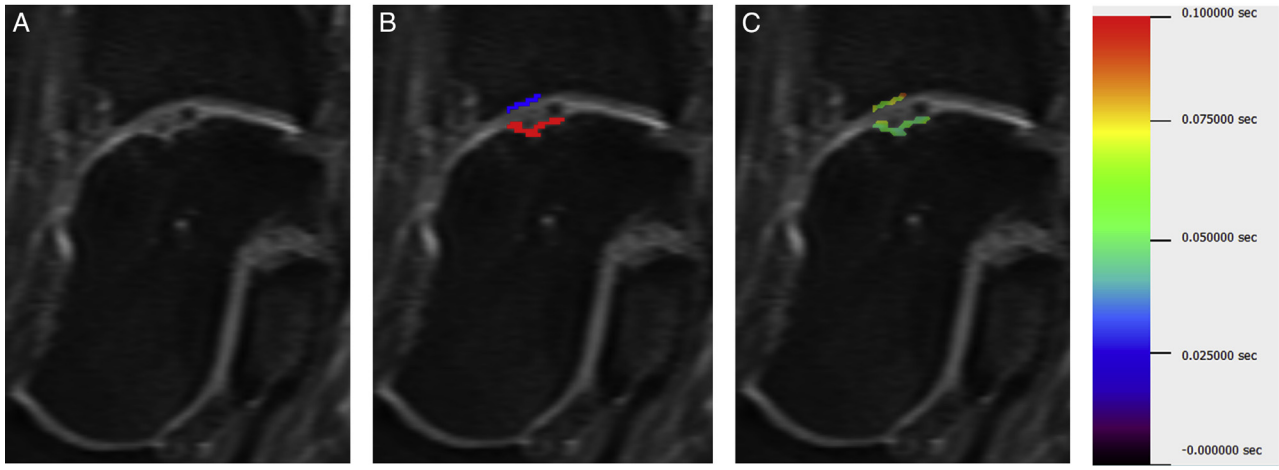

Fig. 2. (*A*) Representative lateral ankle magnetic resonance image at 7 Tesla demonstrating talar osteochondral lesion of subject 6; (*B*) segmented talar osteochondral lesion *(red)* and corresponding tibial lesion *(blue)*; and (*C*) the corresponding T2 relaxation color map.

Table 2
T2 relaxation times from 7 Tesla MRI of the ankle after allograft with respect to the talar lesion and normal talar cartilage

Pt. No.	Talar Lesion T2 Relaxation Time (ms)	95% CI (ms)	Normal Talar T2 Relaxation Time (ms)	95% CI (ms)
1	66.18 ± 7.49	51.21 to 81.16	65.86 ± 11.04	43.79 to 87.93
2	39.94 ± 2.94	34.06 to 45.82	30.23 ± 4.46	21.31 to 39.14
3	119.85 ± 37.44	44.97 to 194.73	74.37 ± 26.96	20.45 to 128.73
4	83.18 ± 19.61	43.97 to 122.38	57.88 ± 11.42	35.03 to 80.73
5	37.54 ± 3.97	29.61 to 45.48	19.98 ± 4.01	11.96 to 27.99
6	55.69 ± 7.42	40.84 to 70.53	50.49 ± 11.52	27.46 to 73.53
7	51.81 ± 9.44	32.93 to 70.68	48.12 ± 6.51	35.09 to 61.14
Mean	64.88 ± 12.22*	NA	49.56 ± 7.81*	NA

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; NA, not applicable; Pt. No., patient number.
Data presented as mean ± standard deviation, unless otherwise noted.
* Statistically significant at $p < .05$.

The present study had several limitations. First, the number of subjects was small. However, for a pilot study, we were still able to detect significant differences in T2 values between talar cartilage repair tissue and native adjacent talar cartilage. Second, we did not scan the patients at 1.5T or 3T and cannot comment on the differences in image quality between standard clinical field strength and ultra-high-field MRI. Third, we did not correlate the MRI outcomes with the clinical outcomes, such as pain and function. In the future, it will be important to correlate the imaging results with the clinical results in a longitudinal study. Fourth, retrospective enrollment and the absence of a control group limited a true comparison between juvenile particulate cartilage and other treatment modalities. A placebo-controlled or head-to-head clinical trial was outside the scope of our pilot study; however, the ideal study in the future would be just such a clinical trial investigating the long-term imaging and clinical outcomes. Fifth, we note that there could be partial volume effects from inclusion of synovial fluid within the segmented regions of interest as tibiotalar cartilage is very thin. We tried to avoid this by focusing more on the deeper cartilage layer. Finally, the interval from surgery to MRI was heterogeneous; thus, future clinical trials should be designed to obtain MRI scans at a designated point or points postoperatively to more consistently assess the T2 relaxation time across patients.

In conclusion, we have demonstrated the feasibility of using T2 mapping of the ankle at 7T to detect altered cartilage biochemical composition in patients who have received a juvenile particulate osteochondral allograft for osteochondral lesions of the talus. If validated in larger longitudinal studies, in particular, clinical trials, T2 mapping could potentially be used in the future to aid surgeons in monitoring and predicting the effectiveness of different types of cartilage repair surgeries and thereby individualize a therapy for a particular patient.

Table 3
T2 relaxation times from 7 Tesla MRI of the ankle after allograft for corresponding tibial region and normal tibial cartilage

Pt. No.	Tibial Lesion T2 Relaxation Time (ms)	95% CI (ms)	Normal Tibia T2 Relaxation Time (ms)	95% CI (ms)
1	128.15 ± 93.74	0 to 315.62	94.27 ± 12.31	69.65 to 118.90
2	41.48 ± 7.28	26.92 to 56.04	42.62 ± 3.64	35.34 to 49.91
3	70.91 ± 12.66	45.60 to 96.22	69.78 ± 5.29	59.19 to 80.37
4	135.03 ± 33.12	68.79 to 201.26	83.20 ± 23.76	35.69 to 130.73
5	54.04 ± 11.53	30.98 to 77.10	38.44 ± 4.66	29.13 to 47.75
6	70.80 ± 10.25	50.31 to 91.29	46.04 ± 1.56	42.93 to 49.16
7	38.59 ± 10.18	18.22 to 58.94	42.31 ± 2.76	36.78 to 47.82
Mean	76.99 ± 31.29*	NA	59.52 ± 7.88*	NA

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; NA, not applicable; Pt. No., patient number.
Data presented as mean ± standard deviation, unless otherwise noted.
* Statistically significant at $p < .1$ but not at $p < .05$.

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