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Articular Cartilage Evaluation After TruFit Plug Implantation Analyzed by Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC)

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Background: Quantitative MRI of articular cartilage has rapidly developed in recent years and provides the clinician with a noninvasive tool to determine the biological consequence of an intervention.

Purpose: To evaluate the quality of intra-articular cartilage, using the dGEMRIC scanning technique, 1 year after TruFit implantation. The hypothesis was that implantation of a TruFit plug does not lead to damage at the opposing articular cartilage.

Study Design: Case series; Level of evidence, 4.

Methods: A total of 13 patients (age, 32 ± 8 years) were evaluated with dGEMRIC at 12 ± 4 months after treatment of an osteochondral lesion by implantation of 1 or multiple TruFit plugs. The dGEMRIC scanning protocol was applied 90 minutes after intravenous Magnevist (0.2 mmol/kg body weight) injection. Different regions of interest (ROIs) were defined: the *femur* cartilage, cartilage directly *surrounding* the implanted TruFit plug, the *TruFit* plug, and the *articulating* and *nonarticulating* tibia cartilage. The average dGEMRIC index (T1gd; magnetic resonance imaging relaxation time per ROI) was calculated by a pixel-by-pixel curve fitting using the Levenberg-Marquardt method. Differences between the mean T1gd of the individual ROI for all patients were tested using analysis of variance with post hoc Bonferroni correction. A P value $<.05$ was considered statistically significant.

Results: The average T1gd of the TruFit ROI (385 ± 74 ms) was comparable with those in the femur (409 ± 49 ms) and surrounding (392 ± 64 ms) ROIs ($P \geq .339$). The average T1gds for the articulating (578 ± 133 ms) and nonarticulating (516 ± 118 ms) ROIs were higher compared with the femur (409 ± 49 ms), surrounding (392 ± 64 ms), and TruFit (385 ± 74 ms) ROIs ($P < .002$), while no difference was observed between the tibia ROIs ($P = .160$).

Conclusion: Implantation of the TruFit plug in osteochondral lesions does not damage the opposing or surrounding surface, and newly formed tissue inside the plug has cartilage-like dGEMRIC characteristics 12 months after implantation. The implantation of synthetic TruFit plugs is safe for the opposing cartilage, an item that is frequently discussed when using such materials to treat focal cartilage defects.

Keywords: dGEMRIC; TruFit; osteochondral; cartilage; regeneration

Quantitative magnetic resonance imaging (MRI) of articular cartilage has rapidly developed in recent years and provides the clinician with a noninvasive tool to determine the biological consequence of an intervention. In this article, we examined the potential use of delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) for evaluation of cartilage quality 1 year after the implantation of a biodegradable scaffold in the treatment of osteochondral defects.

Glycosaminoglycans (GAGs) and type II collagen are the main components of the articular cartilage matrix and determine the compressive stiffness of the tissue. Throughout the process from healthy toward generalized cartilage degeneration, GAGs are released from the matrix. This causes tissue softening and, under continued loading, breakdown of the collagen network. Therefore, a method for noninvasive, nondestructive quantitative evaluation of the concentration of GAGs in articular cartilage would be of great value for

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tracking disease progression and could assist in the diagnostic algorithm. Furthermore, such a technique could also be used to evaluate the success of a regenerative intervention and its influence on other cartilage surfaces in the knee.

The dGEMRIC technique has been introduced as a way of enabling quantified analysis of the GAGs in articular cartilage.[1] The negatively charged side chains in GAG molecules provide the articular cartilage matrix with a negative net charge resulting in a fixed charged density (FCD). The FCD in articular cartilage, which is thus a measure for the GAG distribution, can be determined indirectly after the administration of the negatively charged T1 MRI–shortening contrast agent gadolinium diethylene triamine pentaacetic acid ($Gd\text{-}DTPA^{2-}$; Magnevist; Bayer Schering Pharma, Berlin-Wedding, Germany). After intravenous injection of Magnevist, the $Gd\text{-}DTPA^{2-}$ anionic molecule will penetrate the cartilage and will distribute over the cartilage matrix inversely proportional to the GAG concentration. Thus, the uptake of $Gd\text{-}DTPA^{2-}$ will be higher in areas with low GAG content, resulting in a shortening of the T1 MRI relaxation time in these areas. The dGEMRIC index (T1gd) represents the MRI relaxation time per region of interest (ROI) and thereby the amount of $Gd\text{-}DTPA^{2-}$ present. Areas with a low T1gd therefore represent low GAG content and vice versa.[13] This technique has been shown to have good in vivo reproducibility and to represent the absolute and depth-dependent GAG content and organization in articular cartilage.[15,16,24] The overall day-to-day coefficient of variation of the T1gd in asymptomatic volunteers was determined to be 5%, whereas it was 4.2% for femur cartilage and 5.5% for tibia cartilage.[14] Recent reports also showed the feasibility of the dGEMRIC technique for evaluating success after cartilage regeneration.[21,22]

Selection of the repair technique for the treatment of focal articular cartilage lesions in the knee is directed by the size of the lesion, extension of the lesion toward or into the subchondral bone, duration of symptoms, and the age and activity level of the patient.[4] The recently developed TruFit BGS plugs (Smith & Nephew, Lakewood, California) are currently not included in these evidence-based treatment algorithms but could become an interesting option for small osteochondral lesions of the femoral condyle. The TruFit plug is a bilayered cylindrical plug composed of the polylactide-co-glycolide (PLG) copolymer, calcium-sulfate, and polyglycolide (PGA) fibers. Cartilage regeneration inside TruFit plugs is most likely instigated by the integration of cells and growth factors derived from the bone marrow that infiltrates the plug. Recently, implantation in the medial femoral condyle and lateral trochlear groove showed good histological cartilage formation after 12 months in a goat model.[23] Also, small case series have shown clinical improvement from baseline to 12 months after implantation.[6,23] However, when larger osteochondral lesions are treated, the bony incorporation of the plug can be delayed, leading to treatment failure.[6] Application of the TruFit plug to patellar defects has been related to modest results at 24-month follow-up.[12] In addition, the cartilage surrounding and opposing an osteochondral graft could be damaged because of direct articulation or increased contact pressures caused by instability of the graft.[7,18]

Therefore, this study aimed to evaluate defect rim degeneration to examine possible effects on the opposing cartilage surfaces and to monitor defect region regeneration using the dGEMRIC technique 1 year after treatment of an osteochondral lesion by TruFit implantation. In addition, the study hypothesizes that implantation of a TruFit plug does not lead to cartilage damage at the opposing cartilage.

MATERIALS AND METHODS

Patients and Surgical Technique

From August 2007 to January 2010, a total of 13 patients (age, 32 ± 8 years) who had been treated with a TruFit implantation for their focal articular cartilage defect agreed to enter this study. The main inclusion criterion was a single osteochondral lesion at the femoral condyle, without lesions at distant locations, suitable to be treated with TruFit implantation. General contraindications for MRI, a known allergic reaction to contrast agents and a history of kidney disease, were criteria for exclusion. All patients were informed about the risks associated with this study, and contraindications were evaluated. Patients were given a minimum of 3 days to consider participation, after which informed consent was obtained. Evaluation of the treatment of focal cartilage lesions using dGEMRIC has been approved by the institutional ethical committee.

All included patients suffered from a symptomatic osteochondral lesion of the knee. In general, the surgical procedure was started with knee arthroscopy to evaluate all knee compartments for further lesions followed by the implantation of the TruFit BGS plug(s) using a mini-arthrotomy. The focal lesion was sized and prepared for TruFit implantation by drilling cylindrical holes in the subchondral bone similar to the diameter of the TruFit plug. Debris from drilling was discarded, and the bony wall of the drilled defect was checked for stability. After this, the TruFit delivery device was used to determine the depth of the defect, and the implant was trimmed accordingly at the bony site of the plug. The TruFit plug was implanted flush with the articular surface, and, again, stability was checked. The whole procedure took approximately 30 minutes and was, in all cases, performed by the same surgeon. Nonweightbearing movement was allowed at the first 4 weeks after surgery. From 4 to 6 weeks after surgery, patients were trained to change from non- to full weightbearing movement. From 6 weeks to 4 months, a gradual increase in knee activity and quadriceps muscle control was stimulated. After this, the patient was allowed to return to his previous sports level.

Cartilage Evaluation by MRI

At 12 ± 4 months after implantation of the TruFit plug(s), the articular cartilage quality was evaluated using an implementation of the dGEMRIC technique. For this, patients were intravenously injected with Magnevist at 0.2 mmol/kg body weight and asked to walk for at least 15 minutes to facilitate uptake of the Magnevist by the

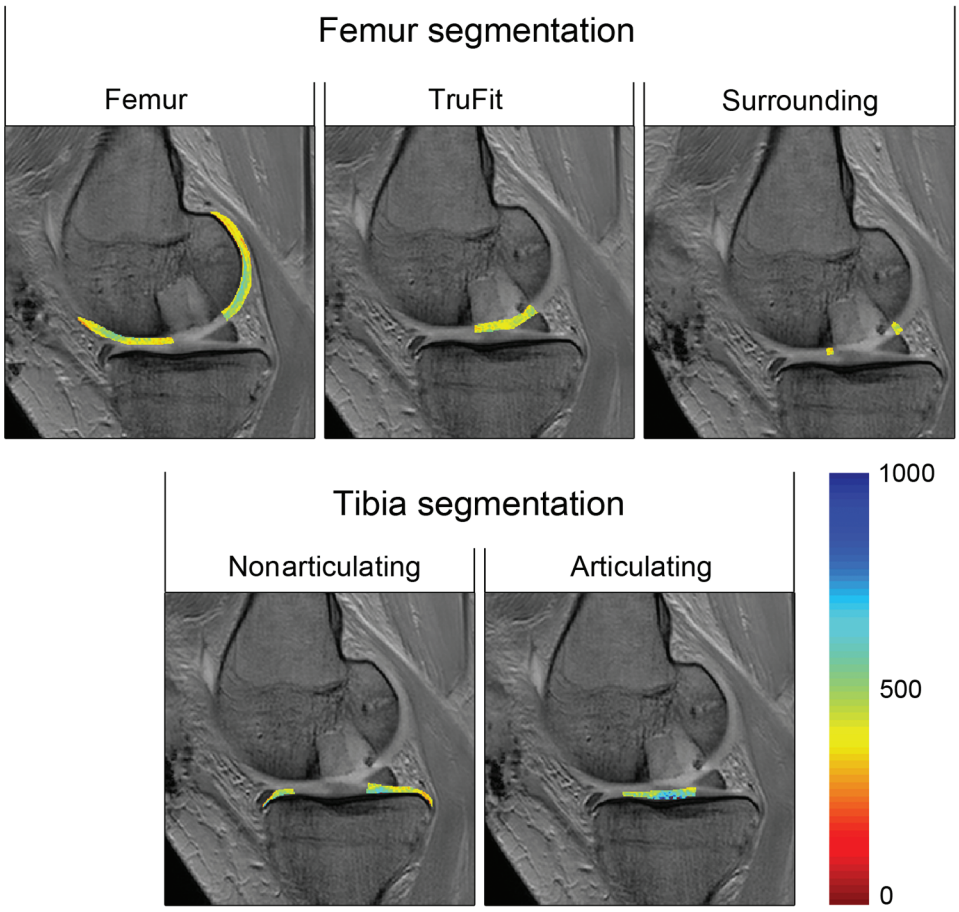

Figure 1. Regions of interest (ROIs). Sagittal magnetic resonance images of postoperative situation when an osteochondritis dissecans lesion of approximately 1.5 cm was treated using 2 TruFit BGS plugs. The bone-plug interface is clearly visible and could be used to define the ROIs. The color bar represents the calculated dGEMRIC index (T1gd), where a high T1gd (1000 ms) is depicted as blue and a low T1gd as red.

articular cartilage. To standardize walking distance and joint loading, all patients were guided through the same route. Scanning on a clinical 1.5-T MRI scanner (Achieva; Philips Healthcare, Best, the Netherlands) took place 90 minutes after intravenous injection using a dedicated 8-element sense knee coil (Philips Healthcare) as a receive coil. The pulse sequence used was a 3-dimensional sagittal transient field echo with 5 different inversion times (50, 150, 350, 650, and 1650 ms), resembling the protocol previously described by McKenzie et al.[15] The acquired voxel size was $0.625 \times 0.625 \times 3$ mm^3; 36 partitions were acquired with an acquisition matrix of 256×232. The repetition time was 10 milliseconds, the echo time was 4.3 milliseconds, and the flip angle was 20°. The average T1gd per ROI was calculated using pixel-by-pixel curve fitting with the Levenberg-Marquardt method using software developed in-house. All ROIs were located in the treated joint compartment.

Five different ROIs were manually drawn on the images obtained from the scanning sequence with a repetition time of 350 milliseconds (Figure 1). At the femoral condyle, the femur, TruFit, and surrounding ROIs were created. The femur ROI was defined by the articular cartilage of the femur condyle at the TruFit implantation compartment, without the site of TruFit implantation (Figure 1). The TruFit ROI was defined as the cartilage site of the implanted TruFit plugs, and the surrounding ROI consisted of the 3-mm ring of articular cartilage that surrounded the TruFit implantation (10 pixels in the x-y direction and 1 slice in both z directions). The nonarticulating and articulating tibia cartilage ROIs were created in the TruFit-implanted knee compartment. The nonarticulating ROI defined the tibia cartilage that did not articulate with the implanted TruFit plugs, while the articulating ROI was described as the tibia cartilage that directly articulated with the implanted TruFit plugs. The ROI segmentations were, with an interval of 2 months, repeated once by the same observer for 5 patients to evaluate the internal consistency and reliability of the segmentation process.

Statistics

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). Differences between the mean T1gd of the individual ROIs for all patients were

tested by a 1-way analysis of variance with post hoc Bonferroni correction. A P value of $<.05$ was considered statistically significant. The internal consistency and reliability of the segmentation process were tested by calculating the Cronbach alpha and intraclass correlation coefficient (ICC). For both the Cronbach alpha and the ICC, values of $>.70$ were considered as acceptable, while values $>.80$ represent excellent internal consistency and reliability.

RESULTS

Defect Characteristics and Patient Follow-up

All osteochondral lesions were located in the femoral condyles (7 medial and 6 lateral) and had an average lesion size of 1.9 ± 0.7 cm^2. Three lesions were true osteochondritis dissecans, while 8 had another cause of osteochondral damage. The defects were filled with, on average, 1.9 ± 0.7 TruFit plugs with a diameter of 7, 9, or 11 mm, depending on the size of the lesion. In total, 4 patients received 1 plug, 6 patients received 2 plugs, and 3 patients received 3 plugs during implantation. No postoperative complications were seen. After a total follow-up of 12 ± 4 months, 2 of the 13 patients still had mild knee complaints, which seemed not to be directly related to the implantation of the TruFit plug. One patient suffered from a chronic Bakers cyst, while the other patient had developed a new condylar cartilage lesion not continuous with the TruFit plug implantation site. All other patients were pain free and had full range of motion at maximum follow-up.

dGEMRIC Analysis

The reliability and internal consistency of the segmentation process was good to excellent, with a Cronbach alpha of .963 and an ICC of .928.

After an average of 12 ± 4 months, the bony part of the TruFit plugs was still visible on the T1-weighted MRI images, while the articular cartilage layer showed a homogeneous T1gd value compared with the surrounding cartilage. The average T1gd of the surrounding ROI (392 ± 64 ms; 95% confidence interval [CI], 346-418 ms) was similar ($P \geq .535$) compared with both the T1gd of the femur ROI (409 ± 49 ms) and the TruFit ROI (385 ± 74 ms). In addition, the average T1gd from the TruFit ROI (385 ± 74 ms; 95% CI, 334-410 ms) did not differ significantly ($P = .339$) from the T1gd values in the femur ROI (409 ± 49 ms; 95% CI, 375-425 ms; Figures 2 and 3).

The articulating ROI showed a similar ($P = .160$) T1gd value (578 ± 133 ms; 95% CI, 490-611 ms) compared with the nonarticulating ROI (516 ± 118 ms; 95% CI, 441-541 ms). Overall, the tibia cartilage T1gd values were higher ($P < .002$) than the femur T1gd values (Figure 2).

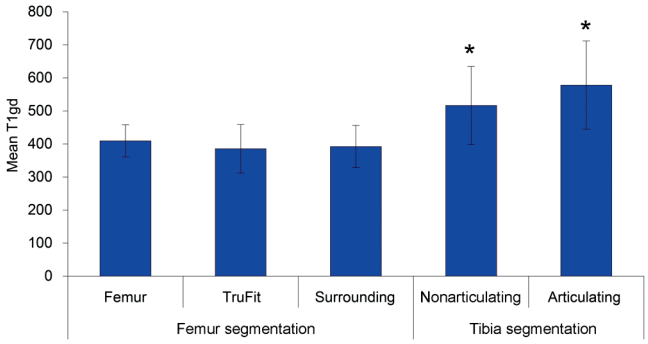

Figure 2. Average T1gd values for all cartilage regions of interest from all patients showing values similar to that in cartilage tissue inside TruFit plugs without additional damage to the opposing articulating cartilage (*$P < .002$).

DISCUSSION

This imaging study evaluated the quality of articular cartilage using a dGEMRIC scan protocol of different anatomic locations in the knee 12 ± 4 months after implantation of a TruFit plug and showed that the T1gd values of the opposing cartilage that directly articulated with the TruFit plug did not differ from nonarticulating cartilage at the tibia. In addition, the T1gd value of the articular cartilage directly surrounding the implanted TruFit plug does not differ from that in the femur cartilage. These results indicate that an implanted TruFit plug does not damage the directly articulating cartilage nor enhance defect rim degeneration. The T1gd values in the cartilage part of the TruFit plug 1 year after implantation were similar to those in the femur cartilage, while the tibia ROIs showed statistical significantly higher T1gd values compared with the femur ROIs.

The TruFit plug is designed to combine the effects of a direct bone and cartilage defect filler as well as structural support to allow regeneration from cells and stimulatory factors derived and absorbed from the bone marrow. Bone marrow stimulation techniques to restore articular cartilage surfaces, such as microfracture, have previously shown good clinical results.[4,17] However, frequently occurring intralesional osteophytes create inferior mechanical stability of the osteochondral tissue, thereby reducing the durability of the regenerated cartilage tissue.[9] The TruFit plug consists of 2 layers that structurally separate the bone from the cartilage tissue, thereby allowing tissue-dependent regeneration, which possibly reduces the development of intralesional osteophytes while addressing the challenge of treating significant osteochondral defects. Therefore, the TruFit plug takes advantage of the regenerative capacity of the cells and proteins present in the bone marrow, while intralesional osteophytes are not likely to develop.

The application of synthetic implants, with or without cells, for the treatment of focal cartilage lesions coincides with a potential concern for additional damage to the directly opposing articulating surfaces. Particularly when such implants are not located flush with the articular surface, they have been associated with increased cartilage erosion and contact pressures at the directly articulating cartilage surfaces.[2,3,7,13] Also, loose bodies from implanted material could initiate damage to articular structures in the knee or cause irritation of the synovial membrane, eventually resulting in synovitis. As presented, the femoral

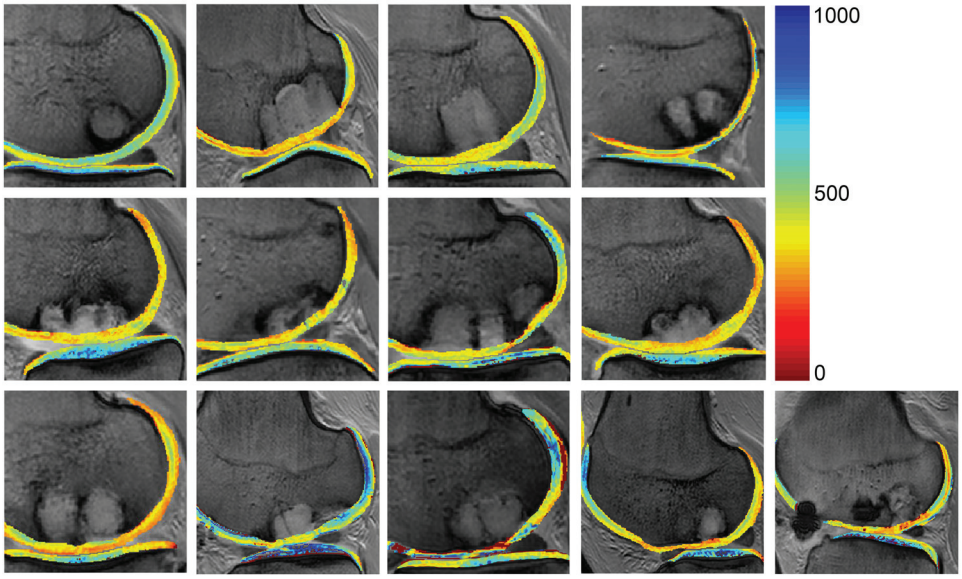

Figure 3. Sagittal delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) images from all included patients showing the TruFit implantation at 12 ± 4 month follow-up. All TruFit plugs were implanted at the load-bearing region of the femoral condyles using an average of 1.9 ± 0.7 plugs per patient. The color bar at the right represents the calculated dGEMRIC index (T1gd) using a continuous color translation of the T1gd from red to blue. Here, red relates to a T1gd of 0 milliseconds, indicative of no glycosaminoglycans (GAGs) present, whereas at the other end, blue represents a T1gd of 1000 milliseconds, indicative of high amounts of GAGs present. The color of the cartilage site of the TruFit plugs ranges from orange to green, representing a T1gd range of 300 to 500 milliseconds between the patients.

TruFit implantation has not been associated with additional damage to the directly articulating tibia cartilage. Also, patients did not suffer from synovitis during our follow-up. This suggests that the implantation of the TruFit in limited amounts for small to median defects is safe and does not inflict any additional damage to the intra-articular environment. In addition, T1gd values at the tibia ROIs were statistically significantly higher compared with the femur ROIs. Whether this indicates higher GAG content in the tibia cartilage compared with the femur sites cannot be concluded as the calculation of the delta relaxation rate ($\Delta R1 = [1/T1(\text{precontrast})] - [1/T1(Gd)]$) would be preferred to draw this conclusion and this study lacks precontrast scans.[1] Baseline T1gd values in healthy volunteers did not show differences between tibia and femur surfaces.[14] Possibly, the presence of a focal lesion affects that particular cartilage surface first before opposing surfaces are affected, leading to lower T1gd values, even after cartilage surgery.

Articular cartilage surrounding a focal lesion has previously been shown to be exposed to increased axial strain because of the higher tendency of the tissue to deform.[5,10,11] This may initiate accelerated matrix damage and tissue loss. Increased tissue deformation could therefore create a noncontinuous cartilage matrix prone to damage. This is also observed after autologous osteochondral transplantation as histological follow-up showed a failed lateral integration of the transplanted cartilage with concomitant severe signs of cartilage degeneration.[18] Also, bony cysts might occur when lateral integration fails, which could, in the long run, lead to a decreased stability of the implanted autologous osteochondral plugs. Our data suggest good lateral integration of the articular part of the TruFit plug without any damage to the articular cartilage surrounding the TruFit plug. Therefore, the newly formed tissue inside the TruFit plug will be less susceptible to accelerated matrix damage owing to increased tissue deformation.

The T1gd index obtained from the newly formed tissue inside the TruFit plug (385 ± 74 ms) is lower than the T1 indices (range, 400-700 ms) from the literature after matrix-associated autologous chondrocyte implantation or microfracturing.[20-22] However, the follow-up in these studies was at least 2 years, while the follow-up presented in this study was 1 year. Further tissue maturation inside the TruFit plug could still take place after 1 year, resulting in higher T1gd values at longer follow-up. In addition, T1gd values in healthy asymptomatic volunteers also show a great variation (range, 428-743 ms) when different dGEMRIC scanning protocols are applied.[14,19] Therefore, direct comparison of obtained T1gd values to reference data from the literature should be interpreted with care as scanning protocols and postprocessing methods differ.

The main weakness of the study is the limited number of included patients and the lack of long-term follow-up. However, considering the hypothesis of the study, these limitations are acceptable in our opinion. Longer follow-up would most likely not have led to the observation of increased damage at the opposing cartilage, as most damage is likely to occur in the first 6 months after the plugs are incorporated in surrounding bone and cartilage. A longitudinal study

with preoperative and long-term (up to 2-5 years) postoperative evaluation using quantitative MRI will provide valuable information on the biology of tissue formation and the quality of newly formed cartilage after TruFit implantation. Also, such studies should be designed for suitable subanalysis on what patient characteristics are related to, or predict, the clinical outcome after implantation of TruFit plugs as MRI lacks a good correlation to clinical outcome.[8] In addition, if quantitative MRI is used, baseline MRI measurements could also be evaluated whether the cartilage quality before surgery influences the quality of eventual repair and clinical outcome.

In conclusion, this study showed that implantation of a TruFit plug does not lead to cartilage defect rim degeneration nor initiate damage at the direct articulating surfaces. Also, newly formed tissue inside the TruFit plug has similar T1 relaxation properties. Whether this suggests articular cartilage–like tissue remains to be seen. Overall, the implantation of a TruFit plug for the treatment of small osteochondral lesions is safe for the directly related articular cartilage structures.

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REFERENCES

1. Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. *Magn Reson Med*. 1999;41(5):857-865.
2. Becher C, Huber R, Thermann H, et al. Effects of a surface matching articular resurfacing device on tibiofemoral contact pressure: results from continuous dynamic flexion-extension cycles. *Arch Orthop Trauma Surg*. 2011;131(3):413-419.
3. Becher C, Huber R, Thermann H, Paessler HH, Skrbensky G. Effects of a contoured articular prosthetic device on tibiofemoral peak contact pressure: a biomechanical study. *Knee Surg Sports Traumatol Arthrosc*. 2008;16(1):56-63.
4. Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med*. 2009;37(suppl 1):148S-155S.
5. Braman JP, Bruckner JD, Clark JM, Norman AG, Chansky HA. Articular cartilage adjacent to experimental defects is subject to atypical strains. *Clin Orthop Relat Res*. 2005;430:202-207.
6. Carmont MR, Carey-Smith R, Saithna A, Dhillon M, Thompson P, Spalding T. Delayed incorporation of a TruFit plug: perseverance is recommended. *Arthroscopy*. 2009;25(7):810-814.
7. Custers RJ, Dhert WJ, van Rijen MH, Verbout AJ, Creemers LB, Saris DB. Articular damage caused by metal plugs in a rabbit model for treatment of localized cartilage defects. *Osteoarthritis Cartilage*. 2007;15(8):937-945.
8. de Windt TS, Welsch GH, Brittberg M, et al. Is magnetic resonance imaging reliable in predicting clinical outcome after articular cartilage repair of the knee? A systematic review and meta-analysis [published online January 30, 2013]. *Am J Sports Med*. doi:10.1177/0363546512473258.
9. Gomoll AH, Madry H, Knutsen G, et al. The subchondral bone in articular cartilage repair: current problems in the surgical management. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):434-447.
10. Gratz KR, Wong BL, Bae WC, Sah RL. The effects of focal articular defects on cartilage contact mechanics. *J Orthop Res*. 2009;27(5):584-592.
11. Gratz KR, Wong BL, Bae WC, Sah RL. The effects of focal articular defects on intra-tissue strains in the surrounding and opposing cartilage. *Biorheology*. 2008;45(3-4):193-207.
12. Joshi N, Reverte-Vinaixa M, Díaz-Ferreiro EW, Domínguez-Oronoz R. Synthetic resorbable scaffolds for the treatment of isolated patellofemoral cartilage defects in young patients: magnetic resonance imaging and clinical evaluation. *Am J Sports Med*. 2012;40(6):1289-1295.
13. Kirker-Head CA, Van Sickle DC, Ek SW, McCool JC. Safety of, and biological and functional response to, a novel metallic implant for the management of focal full-thickness cartilage defects: preliminary assessment in an animal model out to 1 year. *J Orthop Res*. 2006;24(5):1095-1108.
14. Mayerhoefer ME, Welsch GH, Mamisch TC, et al. The in vivo effects of unloading and compression on T1-Gd (dGEMRIC) relaxation times in healthy articular knee cartilage at 3.0 Tesla. *Eur Radiol*. 2010;20(2):443-449.
15. McKenzie CA, Williams A, Prasad PV, Burstein D. Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5T and 3.0T. *J Magn Reson Imaging*. 2006;24(4):928-933.
16. Multanen J, Rauvala E, Lammentausta E, et al. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. *Osteoarthritis Cartilage*. 2009;17(5):559-564.
17. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy*. 2003;19(5):477-484.
18. Tibesku CO, Szuwart T, Kleffner TO, et al. Hyaline cartilage degenerates after autologous osteochondral transplantation. *J Orthop Res*. 2004;22(6):1210-1214.
19. Tiderius CJ, Olsson LE, Nyquist F, Dahlberg L. Cartilage glycosaminoglycan loss in the acute phase after an anterior cruciate ligament injury: delayed gadolinium-enhanced magnetic resonance imaging of cartilage and synovial fluid analysis. *Arthritis Rheum*. 2005;52(1):120-127.
20. Trattnig S, Mamisch TC, Pinker K, et al. Differentiating normal hyaline cartilage from post-surgical repair tissue using fast gradient echo imaging in delayed gadolinium-enhanced MRI (dGEMRIC) at 3 Tesla. *Eur Radiol*. 2008;18(6):1251-1259.
21. Trattnig S, Marlovits S, Gebetsroither S, et al. Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) for in vivo evaluation of reparative cartilage after matrix-associated autologous chondrocyte transplantation at 3.0T: preliminary results. *J Magn Reson Imaging*. 2007;26(4):974-982.
22. Vasiliadis HS, Danielson B, Ljungberg M, McKeon B, Lindahl A, Peterson L. Autologous chondrocyte implantation in cartilage lesions of the knee: long-term evaluation with magnetic resonance imaging and delayed gadolinium-enhanced magnetic resonance imaging technique. *Am J Sports Med*. 2010;38(5):943-949.
23. Williams RJ, Gamradt SC. Articular cartilage repair using a resorbable matrix scaffold. *Instr Course Lect*. 2008;57:563-571.
24. Xia Y, Zheng S, Bidthanapally A. Depth-dependent profiles of glycosaminoglycans in articular cartilage by microMRI and histochemistry. *J Magn Reson Imaging*. 2008;28(1):151-157.