

Graft Hypertrophy After Third-Generation Autologous Chondrocyte Implantation Has No Correlation With Reduced Cartilage Quality

Matched-Pair Analysis Using T2-Weighted Mapping

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Background: Graft hypertrophy is common after matrix-based autologous chondrocyte implantation (ACI) in the knee joint. However, it is not clear whether graft hypertrophy is a complication or an adjustment reaction in the cartilage regeneration after ACI.

Purpose: To analyze the cartilage quality of the ACI regeneration with graft hypertrophy using T2-weighted mapping.

Study Design: Cohort study; Level of evidence, 2.

Methods: A total of 91 patients with isolated cartilage defects (International Cartilage Repair Society [ICRS] grade III-IV) of the knee were treated with Novocart 3D, a third-generation, matrix-based, ACI procedure in the knee joint. All patients were evaluated with a standardized magnetic resonance imaging protocol after 3, 6, 12, 24, 36, and 48 months postoperatively. For morphological and biochemical assessment, the T2-weighted relaxation times of the ACI grafts as well as the healthy surrounding cartilage were determined. The results of the 20 patients with graft hypertrophy (hypertrophic group) were compared with the results of 21 matched patients without graft hypertrophy (nonhypertrophic group) after ACI. Match-paired analysis was performed by comparison of age, defect size, and body mass index.

Results: The T2-weighted relaxation times of the ACI graft showed significant improvement, with values decreasing from 52.1 milliseconds to 33.3 milliseconds after 48 months. After 12 months, the T2-weighted relaxation times were constant and comparable with the healthy surrounding cartilage. Graft hypertrophy was seen in 22% ($n = 20$) of the patients who underwent ACI. A significant difference in T2-weighted relaxation times between the hypertrophic and nonhypertrophic ACI grafts could not be found except after 36 months (hypertrophic T2-weighted relaxation time/nonhypertrophic T2-weighted relaxation time: 3 months, 48.0/56.4 ms, $P = .666$; 6 months, 45.6/42.5 ms, $P = .280$; 12 months, 39.3/34.7 ms, $P = .850$; 24 months, 34.8/32.2 ms, $P = .742$; 36 months, 34.6/38.2 ms, $P = .030$; 48 months, 34.2/32.3 ms, $P = .693$).

Conclusion: The T2-weighted relaxation time of the ACI graft cartilage showed significant improvements over the observation period of 4 years postoperatively. After 2 years, graft maturation was completed. Graft hypertrophy after ACI was seen in 22% of the patients. Reduced cartilage quality could not be found in patients with graft hypertrophy after ACI.

Keywords: ACI; graft hypertrophy; T2-weighted relaxation time; cartilage defect

Autologous chondrocyte implantation (ACI) was established in Sweden in the late 1980s by Brittberg and others^{3,4} and published for the first time in 1994. In the so-called first-generation ACI, a periosteal flap was used

to cover the implanted autologous chondrocytes. In second-generation ACI, the chondrocytes were covered with a collagenous flap. Currently, a matrix-based ACI is most frequently used, which is referred to as third-generation ACI. In matrix-based ACI, the chondrocytes are seeded in a collagenous matrix and are then fixed in the defected cartilage.

The majority (88.5%) of post-ACI complications, which are determined by arthroscopy or magnetic resonance imaging (MRI), can be divided into 4 groups: graft

hypertrophy, poor healing of the ACI graft onto the surrounding healthy cartilage, poor quality of the ACI graft, and graft delamination.¹⁹

Graft hypertrophy after ACI in the knee joint was most frequently observed in the first-generation ACI, which used a periosteal flap for coverage.^{10,25} The use of the second-generation ACI, which substituted the periosteal flap with a type I or III collagen membrane, resulted in a significant decrease in observed graft hypertrophy.^{8,12} This leads to the assumption that the periosteal flap is the cause of graft hypertrophy. However, graft hypertrophy is still observed with third-generation ACI without affecting the clinical outcome.²⁶

The question arises whether there is a difference in cartilage quality between ACI grafts with or without graft hypertrophy. To answer this question, we analyzed ACI graft regeneration using MRI examinations and determined T2-weighted relaxation times with T2-weighted mapping, which is an established method for the assessment of cartilage quality.^{5,18,32} We performed a prospective study, determining the T2-weighted relaxation times at follow-up of 4 years after third-generation ACI with determination of the graft hypertrophy.

The aim of the present study was to assess cartilage quality of the implanted ACI graft in the knee joint in patients with graft hypertrophy. Our hypothesis was that graft hypertrophy of matrix-based ACI has equal cartilage quality in the T2-weighted relaxation time values compared with the ACI graft without graft hypertrophy.

METHODS

Patients

With institutional review board approval, a total 91 patients were included in this study, consisting of 39 women (42.9%) and 52 men (57.1%). All patients were treated between 2004 and 2011 with Novocart 3D (TETEC AG), a third-generation ACI. The ACI procedure and rehabilitation were performed as described in a previous study.²³ The inclusion criteria were full-thickness cartilage defects of grades III or IV according to the International Cartilage Repair Society classification, defect size between 2 and 15 cm², patient age between 16 and 50 years, and intact menisci and ligaments with a regular mechanical axis (<5° malalignment). Patients with osteoarthritis of the knee, joint instability, arthritis, corresponding chondral defects, or more than 2 focal cartilage defects were excluded from the study.

Graft Hypertrophy

The radiological evaluation was performed with an MRI examination of the knee using a 1.5-T device (Magnetom

TABLE 1
Overview of the MRI Examination Protocol^a

Sequences	Time, min:s
1. PD TSE fs coronal 384 matrix	3:50
2. T1-weighted coronal 384 matrix	2:36
3. PD TSE fs sagittal 384 matrix	3:50
4. PD TSE fs axial 384 matrix	4:37
5. T1-weighted FLASH 3D WE sagittal	5:18
6. T2-weighted MAP coronal or axial	12:50
7. T1-weighted FLASH 3D WE coronal or axial	3:03
<i>After injection of contrast agent:</i>	
8. T1-weighted coronal fs 384 matrix	2:36
9. T1-weighted axial fs 384 matrix	2:53

^a3D, 3-dimensional; FLASH, fast low-angle shot; fs, fat saturation; MRI, magnetic resonance imaging; PD, proton density; TSE, turbo spin echo; WE, water excitation.

Avanto, Sonata, Symphony; Siemens Medical Solutions). The MRI examinations were conducted at 3, 6, 12, 24, 36, and 48 months postoperatively based on a standardized protocol including a proton density-weighted sequence (Table 1). The data were collected using the software Syngo (Siemens Medical Solutions).

To identify patients with hypertrophic ACI grafts, the graft thickness was measured in a blinded fashion by an experienced orthopaedic surgeon and a radiologist specializing in musculoskeletal assessment (T.N.).

The thickest areas of the ACI grafts were measured in 3 regions, and the thickness of the healthy surrounding cartilage was measured in the same manner. A mean value was calculated from the 3 measurements. Subsequently, the relative graft thickness was calculated as a ratio between the ACI graft thickness and the thickness of the healthy surrounding cartilage. This relative graft thickness was used to classify graft hypertrophy according to Kreuz et al¹⁵ (grade 1, <125%; grade 2, <150%; grade 3, <200%; grade 4, >200%) (Figure 1). To compare the results of the MRI evaluation of the hypertrophic group, a matched-pair nonhypertrophic group was formed from the database. The criteria for pairwise matching were age, defect size (cm²), and body mass index (BMI; kg/m²). The International Knee Documentation Committee (IKDC) subjective evaluation form was used to evaluate clinical outcomes.

T2-Weighted Relaxation Time

The acquired Digital Imaging and Communications in Medicine (DICOM) data sets were used to segment the cartilage into 3 images. Articular cartilage was segmented in the fast low-angle shot (FLASH) sequence by use of the in-house software PaCaSe.¹³ After segmentation, the cartilage plate

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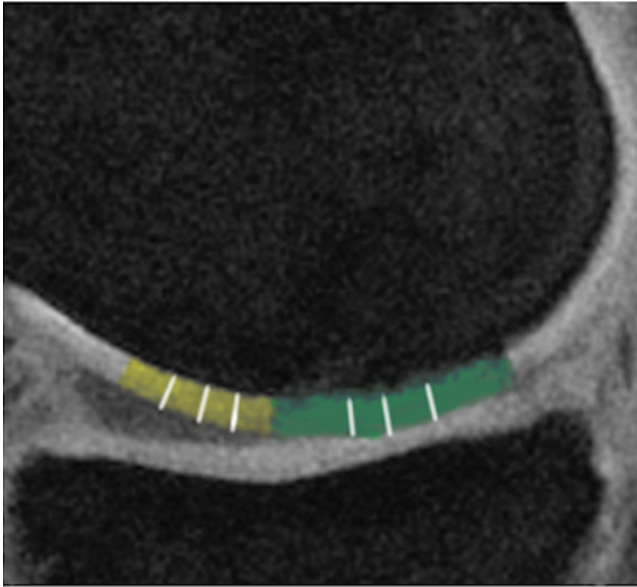


Figure 1. Determination of relative graft thickness of the autologous chondrocyte implantation (ACI) grafts at the femur in a T1-weighted, fast low-angle shot, 3-dimensional sagittal sequence. Green shading, ACI graft; yellow shading, healthy surrounding cartilage.

was reconstructed 3-dimensionally with the overlay of the segmentation sequences with the multiecho data sets. Manual corrections were performed when the water excitation sequences and the multiecho sequences differed due to movement of the patients during MRI examination.

For the calculation of T2-weighted relaxation time, PMI software was used.²⁹ The segmented cartilage was subdivided into 3 zones from the subchondral bone to the cartilage surface. Nine further subdivisions were made from the medial to lateral border. A total of 27 regions of interest, with 70 picture elements per region of interest for each cartilage plate, were created. The T2-weighted relaxation times were expressed as a mean value per segmentation layer of the segmented 3 consecutive slices.

Statistical Analysis

The T2-weighted relaxation times at each time point were assessed according to the age or the sex of the patient, graft location, defect size, and hypertrophy grade by random intercept models. These models were fitted with the MIXED procedure of SAS version 9.2 for Linux (SAS Institute). The *t* test was used to compare the hypertrophic and nonhypertrophic groups. To compare the T2-weighted relaxation times at different control points, nonparametric tests were used depending on the sample. For independent samples, the Whitney *U* test was used. The Wilcoxon test was used in connected samples. The tests were carried out with IBM SPSS Statistics 21. The level of statistical significance was set at $P < .05$.

RESULTS

The mean patient age was 34.4 years (SD, 12.2 years). The mean BMI was 25.9 kg/m² (SD, 4.3 kg/m²). The cartilage defects had a mean size of 5.4 cm² (SD, 2.6 cm²) (Table 2). The location of the cartilage defects was at the medial femoral condyle ($n = 44$, 48%), lateral femoral condyle ($n = 6$, 7%), and patella ($n = 41$, 45%). Two patients missed the 3-month follow-up and 1 patient the 6-month follow-up. No one missed the 12-month follow-up. Two patients missed the 24-month follow-up, 7 patients the 36-month follow-up, and 8 patients the 48-month follow-up.

Graft Hypertrophy

The development of graft hypertrophy was found on MRI examination of 20 patients (the hypertrophic group). This corresponds to a total graft hypertrophy rate of 22%. In 12 patients (60%), the affected graft was located at the medial femoral condyle ($n = 10$; 50%) and lateral femoral condyle ($n = 2$; 10%). In 8 patients (40%), graft hypertrophy occurred in the medial patella (5; 25%) and lateral patella (3; 15%).

New occurrences of graft hypertrophy were found up to 24 months postoperatively. Fifteen patients (75%) developed graft hypertrophy in the first year after ACI. In 5 patients (25%), a new graft hypertrophy could be detected 24 months postoperatively.

In the hypertrophic group, 75% ($n = 15$) of patients had grade 1 graft hypertrophy. In 25% of patients ($n = 5$), grade 2 graft hypertrophy was detected. A de novo development of grade 3 graft hypertrophy was not observed. One patient (5%) who had a grade 2 graft hypertrophy after 12 months went on to develop a grade 3 graft hypertrophy after 24 months. After 36 months postoperatively, this patient had a grade 1 graft hypertrophy. The individual parameters analyzed (BMI, age, sex, and defect size/localization) were not found to influence the occurrence of graft hypertrophy.

Relative Graft Thickness

In the observed postoperative course of 4 years, we found a significant difference in the development of graft thickness of the ACI grafts in patients with graft hypertrophy ($n = 20$; 22%) and those without graft hypertrophy ($n = 21$; 78%). In the first MRI follow-up after 3 months, no relevant difference was found between the hypertrophic (94% relative graft thickness compared with the healthy surrounding cartilage) and the nonhypertrophic ACI grafts (86%). After 24 months, a significant difference was detected ($P = .005$). The hypertrophic group had a maximum mean graft thickness of 124%, with a total increase in graft thickness of 32% in the postoperative course. In comparison, the nonhypertrophic group had a graft thickness of 90% after 24 months (Table 3).

In the following course after 24 months, we found decreasing graft thickness with normalization at the end of the observation period. A significant difference between

TABLE 2
Overview of the Patient Collective^a

	Entire Patient Collective	Hypertrophic Group	Nonhypertrophic Group
No. of patients	91	20	21
Body mass index, kg/m ²	25.9 ± 4.3 (19.0-38.3)	24.7 ± 3.9 (19.0-32.1)	26.3 ± 4.5 (19.6-35.3)
Age, years	34.4 ± 12.2 (11-66)	33.7 ± 12.9 (12.0-57.8)	35.2 ± 12.3 (17.3-66.0)
Defect size, cm ²	5.4 ± 2.6 (2.0-15.0)	5.8 ± 2.7 (2.0-15.0)	5.3 ± 2.9 (4.0-12.0)

^aAll values except for number of patients are expressed as mean ± SD (range).

TABLE 3
Overview of the Development of Relative Graft Thickness in the Hypertrophic and Nonhypertrophic Groups

Follow-up	Hypertrophic Group ^a	Nonhypertrophic Group ^a
3 months	94	89
6 months	106	90
12 months	119	89
24 months	124	90
36 months	120	88
48 months	116	89

^aValues for relative graft thickness are expressed as percentage of the healthy surrounding cartilage.

the hypertrophic group and the nonhypertrophic group was found after 24 months. The nonhypertrophic group showed no relevant change of the graft thickness during the entire observation period (Figure 2).

Clinical Evaluation

The patients included in our study showed significantly higher IKDC scores after 6, 12, 24, 36, and 48 months post-operatively compared with the preoperative findings. The mean IKDC score was 38.2 (SD, 22.2; range, 2.3-99.6). The mean IKDC score increased to 59.8 (SD, 22.0; range, 13.8-93.1) after 48 months. We found no significant differences in IKDC scores between the hypertrophic group (preoperative, 37.4; 6 months, 49.9; 12 months, 51.2; 24 months, 55.1; 36 months, 51.6; 48 months, 56.4) and the nonhypertrophic group (preoperative, 39.1; 6 months, 51.2; 12 months, 57.1; 24 months, 59.6; 36 months, 59.9; 48 months, 61.9) during the course of the entire observation period (preoperative, $P = .728$; 6 months, $P = .830$; 12 months, $P = .393$; 24 months, $P = .558$; 36 months, $P = .207$; 48 months, $P = .484$).

T2-Weighted Relaxation Time

The T2-weighted relaxation times of all ACI grafts were 52.1 milliseconds after 3 months. In the course of the study, we detected a significant reduction of T2-weighted relaxation time by 36%—to 33.3 milliseconds—after 48

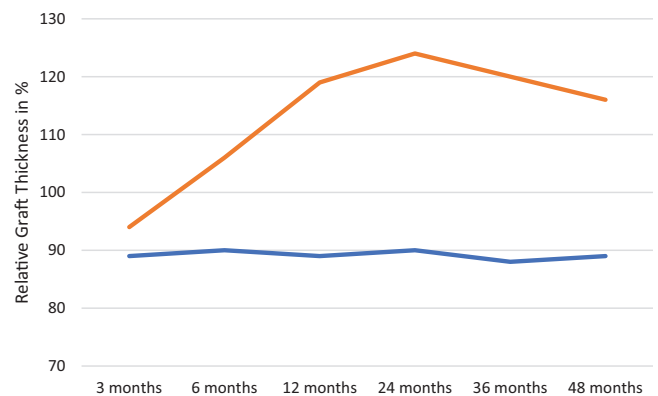


Figure 2. Development of relative graft thickness in the hypertrophic (top line) and nonhypertrophic (bottom line) groups.

months ($P = .000$) compared with the T2-weighted relaxation time after 3 months (Table 4).

In a matched-pair analysis, we analyzed the T2-weighted relaxation times of the hypertrophic grafts ($n = 20$) and the nonhypertrophic grafts ($n = 21$). No significant difference ($P > .05$) between the hypertrophic and the nonhypertrophic grafts was found after 6, 12, and 24 months (Table 5).

After 36 months, a significant difference was found ($P = .03$). However, this difference was not noticeable after 48 months. At the end of the follow-up, an absolute difference of the T2-weighted relaxation time of 1.9 milliseconds was found in the comparison of the two groups, without significant difference between the two groups (Figure 3). No correlation was found regarding the T2-weighted relaxation times and the grade of graft hypertrophy.

DISCUSSION

The most important finding of the present study was that graft hypertrophy after third-generation ACI is a transient phenomenon, as we noted equal T2-weighted relaxation times compared with the nonhypertrophic ACI grafts over the observation period of 4 years. Graft hypertrophy can therefore be seen as an adjustment reaction after third-generation ACI.

TABLE 4
Overview of the T2-Weighted Relaxation Times of All ACI Grafts and the Healthy Surrounding Cartilage

Follow-up	All ACI Grafts ^a	All Healthy Surrounding Cartilage ^a	P Value
3 months	52.1 ± 18.5	33.2 ± 6.9	.018 ^b
6 months	44.1 ± 13.0	31.8 ± 4.8	.020 ^b
12 months	37.1 ± 8.0	31.0 ± 4.7	.163
24 months	33.6 ± 7.3	31.4 ± 5.1	.825
36 months	36.4 ± 10.6	29.9 ± 5.5	.300
48 months	33.3 ± 8.2	31.6 ± 3.3	

^aValues expressed in milliseconds as mean ± SD. ACI, autologous chondrocyte implantation.

^bAfter 12 months, no significant differences between the ACI grafts and the healthy surrounding cartilage were found.

TABLE 5
T2-Weighted Relaxation Times of the Autologous Chondrocyte Implantation Grafts in the Hypertrophic and Nonhypertrophic Groups

Follow-up	Hypertrophic Group ^a	Nonhypertrophic Group ^a	P Value
3 months	48.0 ± 18.4	56.4 ± 18.2	.666
6 months	45.6 ± 16.3	42.5 ± 8.6	.280
12 months	39.3 ± 8.3	34.7 ± 7.3	.850
24 months	34.8 ± 7.7	32.2 ± 7.0	.742
36 months	34.6 ± 5.7	38.2 ± 13.9	.03 ^b
48 months	34.2 ± 7.4	32.3 ± 9.1	.693

^aValues expressed in milliseconds as mean ± SD.

^bAfter 36 months, a significant difference was found ($P = .03$). However, this difference was not noticeable after 48 months.

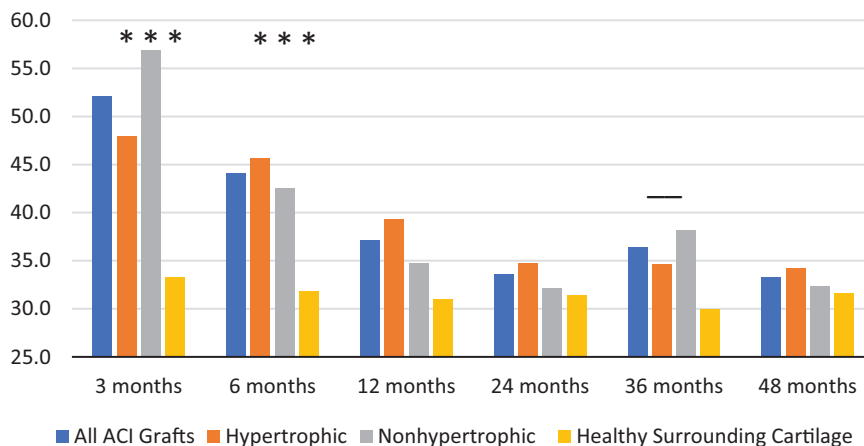


Figure 3. Development of T2-weighted relaxation times (ms) in all autologous chondrocyte implantation (ACI) grafts, in hypertrophic and nonhypertrophic groups. After 3 and 6 months, significantly different T2-weighted relaxation times were found compared with the healthy surrounding cartilage ($*P < .005$). After 6 months, no significant differences were observed. No differences between the hypertrophic and nonhypertrophic grafts were found after 3, 6, 12, 24, and 48 months. After 36 months, a difference was observed with a temporary increase in the T2-weighted relaxation times of the nonhypertrophic group (line).

Graft hypertrophy after ACI is often observed in the postoperative course and is seen as a potential cause of postoperative pain, which can lead to an operative revision surgery. In previous studies, no worse clinical results were observed in patients with graft hypertrophy after third-generation ACI.^{26,34} These results could be confirmed by the findings of the present study. However, less knowledge

is available about the cartilage quality of the ACI grafts in patients with graft hypertrophy. For the first time, we analyzed hypertrophic ACI grafts with T2-weighted relaxation times in a 4-year observation.

In the present prospective study, a radiological evaluation of the implanted, cell-seeded collagenous scaffolds was carried out with standardized MRI examination in

postoperative follow-up. For comparative reasons, all patients were treated with the same third-generation ACI product (Novocart 3D).

MRI examination after ACI is an established and suitable method for analyzing the healing of ACI grafts for cartilage regeneration.^{7,14,28} The T2-weighted relaxation time is a complex method for quantitative analysis of ACI cartilage maturation and has been used in previous studies.^{22,27,31} To identify patients with graft hypertrophy, we measured the relative graft thickness according to the method established by Kreuz et al.¹⁵

For the assessment of hyaline articular cartilage, biochemical MRI (eg, T2-weighted relaxation time) is a more sensitive method for detecting chondral lesions than conventional magnetic resonance tomography.⁹ Determination of T2-weighted relaxation time and the use of T2-weighted mapping are already regularly used in the context of cartilage repair procedures.^{5,6,18,22,27}

The incidence of graft hypertrophy in the present study was 22%. Previous studies have found similar incidences of graft hypertrophy. Zak et al³⁴ found an incidence of 24% after 6 months. In another study, the graft hypertrophy incidence in patients with third-generation ACI was 27%.²¹ The incidence of graft hypertrophy in other studies in the literature has ranged from 9% to 40%.^{1,17,35} All observed graft hypertrophies occurred within 24 months after the operation; 75% of the diagnosed graft hypertrophies occurred in the first year postoperatively.

Our detailed analysis of hypertrophic and nonhypertrophic patients shows that the hypertrophic patients had a significant increase in graft thickness after 12 to 24 months. The nonhypertrophic grafts, however, showed no additional growth between 12 and 24 months. After this period, the relative graft thickness declined in the hypertrophic group.

In this study, a majority of cases of graft hypertrophy were grades 1 and 2. Clinical results in the literature did not show worse outcomes.^{30,34} A grade 3 graft hypertrophy was observed in only 1 patient in the current study, and no revision surgery was performed. No cases of grade 4 graft hypertrophy were observed. In previous studies, more cases with a higher grade of graft hypertrophy have been observed with the use of a periosteal flap (Kreuz et al¹⁵: grade 1, 20.7%; grade 2, 37.9%; grade 3, 24.1%; grade 4, 10.3%).

The causes for graft hypertrophy after ACI remain unclear. Previously, osteochondritis dissecans and acute trauma were seen as risk factors.³⁰ Henderson et al¹¹ observed a possible influence of the defect size and graft localization in first-generation ACI using a periosteal flap. It was thought that the BMI, the patient's age or sex, the defect size, and the defect location (femoral condyle/patella) were risk factors that could lead to the development of graft hypertrophy in the postoperative course. In the present study, we found no influence of the analyzed parameters (BMI, age, sex, and defect size/localization) on the occurrence of graft hypertrophy.

We suggest that the cause of graft hypertrophy after third-generation ACI without periosteal flap seems to be intrinsic. Li et al¹⁶ found that static compressive stress

had a relevant influence on chondrocyte proliferation *in vitro*, which possibly may influence graft hypertrophy after cartilage repair procedures. The assumption that graft hypertrophy is a temporary adaptation process might be affirmed by the results of our study. At the end of the observation period, we found a mild relative graft hypertrophy of 116% in the hypertrophic group without complaints, which supports this assumption.

The T2-weighted values for healthy cartilage and cartilage transplants were measured postoperatively between 30 and 34 milliseconds for 24 to 48 months, parameters which were described by Dunn et al⁵ and Nissi et al.²⁴ One major finding of this study is that we did not find a significant difference in the T2-weighted relaxation times between hypertrophic and nonhypertrophic ACI grafts over the course of the entire observation period. We found no evidence for different amounts of collagen, a different collagen fiber course, or increased water content in hypertrophic ACI grafts compared with nonhypertrophic ACI grafts. Only once, after 36 months, was a temporary difference detected between the hypertrophic and the nonhypertrophic groups. The single, observed significant difference of the T2-weighted relaxation time might have been caused by the increased thickness of the hypertrophic group before 36 months with an intermediate content of water of the hypertrophic grafts. After 36 months, no significant differences were observed, suggesting that the overwhelming growth of the hypertrophic grafts had ended.

This observation coincides with the published results of Niemeyer et al.²⁰ In their case report, no significant difference could be found in the histological analysis of a hypertrophic ACI graft of a 49-year-old female patient. The authors concluded that graft hypertrophy did not cause histological changes with hypertrophic chondrocytes.

A defective collagen network, which can be assessed with T2-weighted relaxation time, is an indicator of defective cartilage tissue.³³ Increased T2-weighted relaxation times for the ACI grafts were seen in general at the beginning of the maturation process, about 6 months after the ACI procedure. A completed maturation process can be found by an adjustment of the T2-weighted relaxation times between the ACI grafts and healthy surrounding cartilage.

For both groups (hypertrophic and nonhypertrophic), we showed an adjustment of the T2-weighted relaxation times in the postoperative course with decreasing standard deviation from 18 milliseconds after 3 months to 7 milliseconds after 48 months postoperatively. This corresponds to a homogenization of the T2-weighted relaxation times in the analyzed groups. This assumption is in agreement with the findings of previous studies.²²

Breinan et al² observed a proliferation of chondrocytes in rabbits during the first 3 months after cartilage cell implantation. A significant difference in T2-weighted relaxation times between the ACI grafts and the healthy surrounding cartilage was seen up to 6 months postoperatively in the current study. Through these findings, we hypothesize that the maturation of the ACI grafts is not completed before 12 months.

One limitation of the study is the lack of histological biopsy specimens of the ACI grafts. An additional histological analysis would improve the results of this study. This analysis could confirm the measurements of T2-weighted relaxation time. Furthermore, it would be interesting to get more information about the cartilage structure and content of problematic ACI graft therapies, such as those that entail graft hypertrophy or postoperative pain.

CONCLUSION

The analysis of T2-weighted relaxation times of all ACI graft cartilage shows significant improvements during the postoperative observation time of 4 years. The T2-weighted relaxation times of the ACI grafts showed similar values compared with normal hyaline cartilage after 12 to 24 months. Graft hypertrophy after matrix-based ACI was seen in 22% of the patients. No differences in T2-weighted relaxation times could be found between patients with or without graft hypertrophy after ACI. Graft hypertrophy seems to be an adjustment reaction that declined in the postoperative course without operative intervention. Hypertrophic ACI grafts show no worse cartilage quality compared with regular ACI grafts.

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