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Am J Sports Med 2012 40: 68 originally published online October 26, 2011
DOI: 10.1177/0363546511424396

The Incidence and Clinical Relevance of Graft Hypertrophy After Matrix-Based Autologous Chondrocyte Implantation

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Background: Graft hypertrophy is the most common complication of periosteal autologous chondrocyte implantation (p-ACI).

Purpose: The aim of this prospective study was to analyze the development, the incidence rate, and the persistence of graft hypertrophy after matrix-based autologous chondrocyte implantation (mb-ACI) in the knee joint within a 2-year postoperative course.

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

Methods: Between 2004 and 2007, a total of 41 patients with 44 isolated cartilage defects of the knee were treated with the mb-ACI technique. The mean age of the patients was 35.8 years (standard deviation [SD], 11.3 years), and the mean body mass index was 25.9 (SD, 4.2; range, 19-35.3). The cartilage defects were arthroscopically classified as Outerbridge grades III and IV. The mean area of the cartilage defect measured 6.14 cm^2 (SD, 2.3 cm^2). Postoperative clinical and magnetic resonance imaging (MRI) examinations were conducted at 3, 6, 12, and 24 months to analyze the incidence and course of the graft.

Results: Graft hypertrophy developed in 25% of the patients treated with mb-ACI within a postoperative course of 1 year; 16% of the patients developed hypertrophy grade 2, and 9% developed hypertrophy grade 1. Graft hypertrophy occurred primarily in the first 12 months and regressed in most cases within 2 years. The International Knee Documentation Committee (IKDC) and visual analog scale (VAS) scores improved during the postoperative follow-up time of 2 years. There was no difference between the clinical results regarding the IKDC and VAS pain scores and the presence of graft hypertrophy.

Conclusion: The mb-ACI technique does not lead to graft hypertrophy requiring treatment as opposed to classic p-ACI. The frequency of occurrence of graft hypertrophy after p-ACI and mb-ACI is comparable. Graft hypertrophy can be considered as a temporary excessive growth of regenerative cartilage tissue rather than a true graft hypertrophy. It is therefore usually not a persistent or systematic complication in the treatment of circumscribed cartilage defects with mb-ACI.

Keywords: cartilage; autologous chondrocyte implantation; graft hypertrophy

Brittberg et al first described the classic autologous chondrocyte implantation (ACI) with a periosteal flap in 1994.[2] Since then, the safety and the efficiency of this method for the treatment of large circumscribed cartilage defects in the knee joint have been verified in numerous long-term studies.[2,19,20,23] Apart from the fact that the technique of ACI is fastidious, the main problem of the ACI was the high rate of graft hypertrophy (GH), which was attributed primarily to the periosteal flap cover. Graft hypertrophy is the most common complication of the classic periosteal flap ACI (p-ACI), with an incidence of 36%.[1,3,10,12,15-17,24] This hypertrophy often results in clinical symptoms, thus resulting in revision surgery with ablation of the hypertrophic cartilage.[17] The matrix-based ACI (mb-ACI) is the advancement of the classic p-ACI technique, where the chondrocytes are seeded on an absorbable matrix. This method has the advantage of a stable and 3-dimensional arrangement of the chondrocytes in the cartilage defect and allows a simplification of the surgical handling. The clinical results of the mb-ACI are comparable with those of the classic ACI.[1,4,9,17] Because the periosteal cover of the defect is not applicable using the mb-ACI technique, we have assumed that the rate of GH is smaller than after p-ACI.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

The American Journal of Sports Medicine, Vol. 40, No. 1
DOI: 10.1177/0363546511424396

The aim of this prospective study was the analysis of the development, the incidence rate, and the persistence of GH after mb-ACI in the knee joint in a 2-year postoperative course. The following hypotheses were postulated: (1) The incidence of GH after mb-ACI is lesser than that reported for p-ACI because periosteal flap coverage is not applied. (2) The necessity of GH treatment should therefore be distinctly less in comparison to p-ACI. The data were retrieved by analyzing the rate of revision arthroscopy because of GH as well as the correlation between GH and the International Knee Documentation Committee (IKDC) score. Our results after mb-ACI surgery were compared with the incidence rate and clinical relevance of GH after p-ACI in the literature.

MATERIALS AND METHODS

Overview

Between 2004 and 2007, a total of 41 patients with 44 isolated cartilage defects of the knee were treated with the mb-ACI technique. The mean age of the patients was 35.8 years (standard deviation [SD], 11.3 years), with a sex ratio of 24 men to 17 women and a mean body mass index (BMI) of 25.9 (SD, 4.2; range, 19-35.3). The cartilage defects were arthroscopically classified as Outerbridge grades III and IV. The mean area of the cartilage defect measured 6.14 cm^2 (SD, 2.3 cm^2). Cartilage defect localizations were distributed as follows: 23 (52.3%) of the cartilage defects treated lay femoral, and 21 (47.7%) lay retropatellar. Excluded were patients with osteoarthrosis of the knee, joint instability, arthritis, corresponding chondral defects, and more than 2 focal cartilage defects.

The following cosurgeries were performed: partial meniscus resection (n = 4), cartilage shaving/smoothing (n = 7), plica resection (n = 1), removal of foreign bodies (n = 4), microfracture (n = 2), spongiosaplasty (n = 6), osteochondritis dissecans (OD) refixation (n = 1), tibial tuberosity transfer (n = 1), high tibial osteotomy (HTO) (n = 1), anterior cruciate ligament (ACL) reconstruction (n = 2), and lateral release (n = 1).

mb-ACI and Rehabilitation

The scaffolds (Novocart 3D, TETEC AG, Reutlingen, Germany) were attached to healthy cartilage with an absorbable Vicryl USP 5-0 suture (Ethicon Inc, Johnson & Johnson, Norderstedt, Germany). Alternatively, in 12 cases (27.3%), the scaffolds were affixed to the bone using pins in cases where a fixation was not possible because of a lack of healthy and stable cartilage tissue. Fibrin glue was not used. After 24 hours of bed rest and drain removal, postoperative after-care treatment of the femoral cartilage defects began using a continuous passive motion (CPM) device on the second postoperative day. With defects on the femoral condyles, weightbearing was limited to 20 kg for 6 weeks, while flexion was increased quickly. Patients with patellar defects were fitted with a knee brace and set to limited flexion of 30° for 2 to 3 weeks. Afterward, flexion was gradually increased. Full weightbearing was allowed with full extension.

Clinical Scores

The International Cartilage Repair Society (ICRS) Cartilage Injury Standard Evaluation Form 2000 was used as a basis for the assessment of subjective and objective clinical parameters as well as the 2000 IKDC Subjective Knee Evaluation Form and the visual analog scale (VAS) for the registration of rest pain and pain after activity. The data were collected preoperatively and postoperatively (after 6, 12, and 24 months), and the results were recorded in the standardized ICRS form. The IKDC and VAS scores used in this study are established and validated scores in the follow-up examination of cartilage regeneration procedures and show a high rate of reliability and reproduction,[11,22] hence the frequent use of these scores in follow-up examinations after p-ACI and mb-ACI.[9,14,17,18,21]

Magnetic Resonance Imaging

A follow-up magnetic resonance imaging (MRI) examination was performed after 3, 6, 12, and 24 months using a 1.5-T machine (Magnetom Sonata, Fa Siemens AG, Erlangen, Germany) with the use of a commercially available circular polarizing 1-channel knee spool in a predetermined protocol. Fast spin echo (dual T2-FSE) and fat saturation gradient echo (3D-GE-FS) sequences were produced. Additionally, proton-weighted sequences as well as T1-weighted fast low angle shot sequence (FLASH) with selective water stimulation was performed. The 3D FLASH sequence is a validated sequence for the measurement of knee cartilage with MRI, as demonstrated by Eckstein et al.[7] These sequences are the same ones as described by Kreuz et al[12] in the evaluation of GH after classic ACI. Graft hypertrophy classification was rated using the scale of Kreuz et al[12] (grade 1 hypertrophy, <125%; grade 2 hypertrophy, <150%; grade 3 hypertrophy, <200%; grade 4 hypertrophy, >200%).

The measurements of the cartilage thickness were done in a blinded fashion by an experienced orthopaedic surgeon and a radiologist who specialized in musculoskeletal radiology. The cartilage and transplant thickness was measured and evaluated in a standardized manner with the software MagicView 1000VB33a/MagicWeb (Fa Siemens Medical Systems, Erlangen, Germany) using DICOM data sets (Digital Imaging and Communications in Medicine, Rosslyn, Virginia). Cartilage defects lying in the condylar region were evaluated using the sagittal planes and retropatellar defects using the axial planes. The thickest area of the graft was measured as well as 3 regions in the adjacent normal cartilage (Figure 1). The standardized graft and healthy cartilage measurements were conducted by determining the mean values of 3 measuring points in the thickest region of the tissue. The ratio between the thickness of the graft and the thickness of the healthy cartilage was determined.

Statistics

The retrieved data were analyzed using the statistics program SPSS (Statistical Package of Social Sciences, Version 18, Chicago, Illinois). The descriptive data were presented

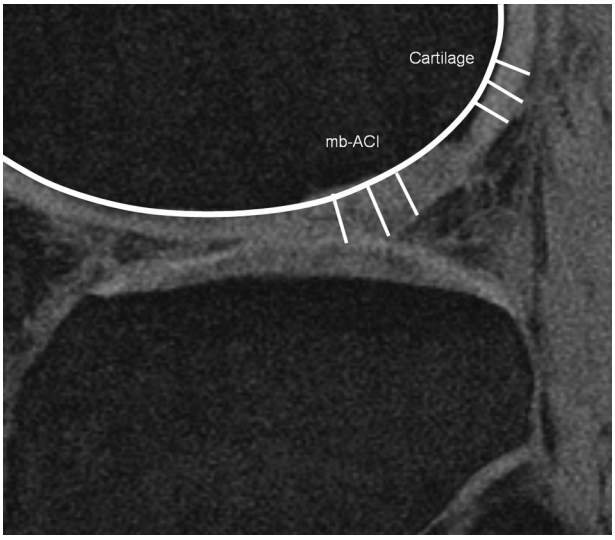

Figure 1. T1-weighted magnetic resonance imaging study of a fast low angle shot sequence (FLASH) of a right knee after 12 months. ''mb-ACI'' shows the 3 measuring points of the hypertrophic graft. ''Cartilage'' shows the 3 measuring points of the normal cartilage.

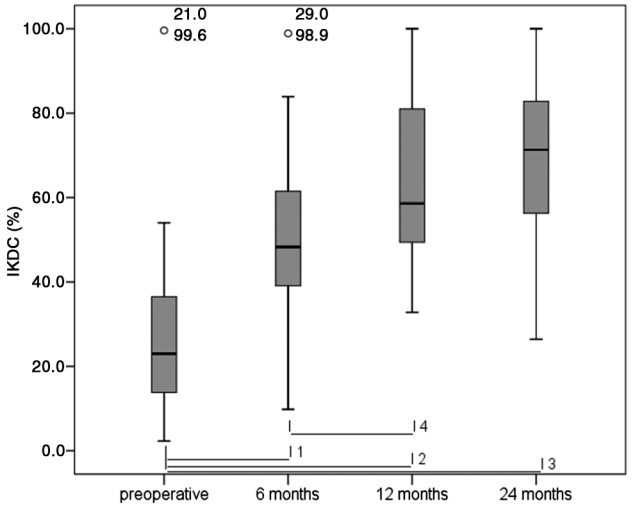

Figure 2. Overview of the clinical International Knee Documentation Committee (IKDC) values with significant improvement after 6, 12, and 24 months in comparison with the preoperative results ([1] $P = .001$, [2] $P = .001$, [3] $P = .001$, and [4] $P = .001$). The IKDC result between the 12th and 24th months was not significant using the Wilcoxon test ([5] $P = .067$).

with absolute and relative frequency of occurrence, mean value, and standard deviation. The coherence between GH and potential influencing factors to the various follow-up examinations was verified with multiple logistic regression analysis. Significant differences between preoperative and postoperative examination times were determined using the Wilcoxon test for dependent samples and the Mann-Whitney U test for independent samples in the comparison of 2 groups at a certain time period. The results were significant if $P < .05$.

RESULTS

Overview of the Clinical Scores

The patients from our collective showed a significantly higher IKDC score postoperatively after 6, 12, and 24 months compared with the preoperative values. The preoperative IKDC value was 28.2% (SD, 18.0%). During the postoperative observation period of 2 years, the mean IKDC value increased to 68.6% (SD, 21.8%), with the greatest significance at 6 and 12 months postoperatively; a positive trend ($P = .067$) was observed between the values of the 12th and 24th months (Figure 2).

Revision

Surgical revision was performed in 8 patients (19.4%). In 5 cases (11.9%), revision was necessary because of arthrofibrosis and in 1 case because of pain without GH, and in 2 cases, another mb-ACI was performed because of graft failure (one because of an early infection). Surgical revisions because of GH were not performed.

Graft Hypertrophy

Eleven patients showed GH postoperatively in our patient collective with a total sum of 44 cartilage defects (Table 1). The GH observed occurred during the first 12 postoperative months. In 8 patients, GH occurred after 6 months, and in 2 patients with femoral cartilage defects, GH was observed after 12 months. No new cases of GH were observed in the follow-up examination after 24 months (Figure 3).

Four patients developed GH grade 1 postoperatively. In 2 patients, GH grade 1 occurred after 3 months, in 2 patients after 6 months, and in 1 patient after 12 months. In all patients with GH grade 1 (100%), a complete GH regression was observed after 24 months.

Graft hypertrophy grade 2 occurred in 7 cases. One patient developed GH grade 2 after 3 months, 5 patients after 6 months, and only 1 patient after 12 months postoperatively. In 1 patient, the GH progressed from grade 1 to grade 2 in a time span of 12 months. In 4 patients, a grade 2 GH persisted in the time span of 2 years. In the other 3 patients, a total regression of a grade 2 GH could be observed (Table 2).

Localization

Cartilage defect localizations were distributed as follows: 23 (52.3%) of the cartilage defects treated were femoral, and 21 (47.7%) were retropatellar. Femoral cartilage damage occurred predominantly on the medial femoral condyle (n = 19), and the other 4 occurred in the lateral femoral condyle. In 3 patients, mb-ACI treatment was performed on 2 cartilage defects lying femoral and retropatellar.

TABLE 1
Patient Overview[a]

	Graft Hypertrophy Grade		
	Grade 0 (No Hypertrophy)	Grade 1 (100%-125%)	Grade 2 (125%-150%)
3 months			
Defects, n (%)	37 (84.1)	2 (4.5)	1 (2.3)
Age, mean (range), y	35.1 (16-50)	45.5 (43-48)	16
Location, n (%)			
Medial femoral condyle	16 (43.2)	1 (50)	0
Lateral femoral condyle	3 (8.1)	0	1 (100)
Retropatellar	18 (48.6)	1 (50)	0
Surgical intervention	0	0	0
6 months			
Defects, n (%)	34 (77.3)	2 (4.5)	6 (13.6)
Age, mean (range), y	36.2 (16-50)	25 (17-33)	32.5 (16-46)
Location, n (%)			
Medial femoral condyle	14 (41.2)	2 (100)	1 (16.7)
Lateral femoral condyle	2 (5.9)	0	2 (33.3)
Retropatellar	18 (52.9)	0	3 (50)
IKDC score, % / average VAS score	50.9%/4.4	58.9%/2.5	48.7%/4.3
Surgical intervention	0	0	0
12 months			
Defects, n (%)	30 (83.3)	2 (5.6)	4 (11.1)
Age, mean (range), y	35.9 (16-50)	47	26.3 (16-46)
Location, n (%)			
Medial femoral condyle	14 (46.7)	1 (50)	0
Lateral femoral condyle	1 (3.3)	0	2 (50)
Retropatellar	15 (50)	1 (50)	2 (50)
IKDC score, % / average VAS score	62.7%/3.3	33.7%/5.0	52.5%/4.5
Surgical intervention	0	0	0
24 months			
Defects, n (%)	29 (87.9)	0	4 (12.1)
Age, mean (range), y	36.1 (16-49)	43	26.3 (16-46)
Location, n (%)			
Medial femoral condyle	13 (44.8)	0	0
Lateral femoral condyle	1 (3.4)	0	2 (50)
Retropatellar	15 (51.7)	0	2 (50)
IKDC score, % / average VAS score	67.7%/3.3	0	68.7%/4.1
Surgical intervention	0	0	0

[a]International Knee Documentation Committee (IKDC); VAS, visual analog scale.

The femoral cartilage defect size was 6.0 cm^2 (SD, 2.2 cm^2) and retropatellar was 6.3 cm^2 (SD, 2.5 cm^2), being almost equivalent (P = .981). There was no relevant difference regarding the BMI and the age of the patient (Table 3).

The frequency of occurrence of GH in the femur and retropatellar was equivalent in all follow-up periods. In patients with retropatellar cartilage damage, 4 cases of GH were observed, where 3 patients developed GH grade 2 and 1 patient developed GH grade 1. Four patients developed femoral GH grade 2, and 3 patients developed femoral GH grade 1. The differences regarding the frequency of various grades of hypertrophy between the femoral and retropatellar localizations were statistically not significant (P = .489).

Correlation Between GH With the IKDC and VAS

During the postoperative follow-up examinations, there was no difference between the clinical results regarding the IKDC score and VAS pain and the presence of GH. Patients with GH grade 1 or 2 averaged a mean IKDC value of 57.0% (SD, 21.2%) after 12 months and 65.7% (SD, 23.9%) after 24 months. Patients without hypertrophy presented a mean IKDC value of 62.7% (SD, 19.2%) after 12 months and 67.7% (SD, 19.1%) after 24 months. No significant differences could be observed in the IKDC and VAS scores in patients with GH grade 1 or 2 (P = .22 after 12 months; P = .803 after 24 months) (Figure 4).

DISCUSSION

Graft hypertrophy is one of the most common complications of p-ACI, with an incidence of 36%,[1,3,10,12,15-17,24] and leads to clinical discomfort as well as surgical revision with abrasion of the hypertrophy.[17] The periosteal flap cover was made responsible for the hypertrophy in p-ACI. The

TABLE 2
Postoperative Course of Graft Hypertrophy

Patient	Gender	Age, y	Defect Localization	Graft Hypertrophy Grade			
				After 3 Months	After 6 Months	After 12 Months	After 24 Months
1	Female	17	Femoral	0	1	0	0
9	Male	16	Femoral	2	2	2	2
10	Male	33	Femoral	0	1	0	0
16	Female	46	Retropatellar	0	2	2	2
17	Female	46	Femoral	0	0	1	0
21	Male	43	Femoral	1	2	0	0
22	Male	24	Femoral	0	0	2	2
24	Male	46	Retropatellar	0	2	0	0
28	Male	25	Femoral	0	2	0	0
34	Female	19	Retropatellar	0	2	2	2
40	Female	48	Retropatellar	1	0	1	0

TABLE 3
Overview of the Localization of Graft Hypertrophy

	Femoral	Retropatellar
No. (%)	24 (54.5)	20 (45.5)
Body mass index, mean ± standard deviation (range)	25.9 ± 4.1 (19-34)	26 ± 4.5 (19.2-35.3)
Age, mean ± standard deviation (range), y	36.4 ± 12.0 (16-50)	35 ± 11.0 (16-49)
Defect size, mean ± standard deviation (range), cm^2	6.0 ± 2.2 (2-10)	6.3 ± 2.5 (4-12)

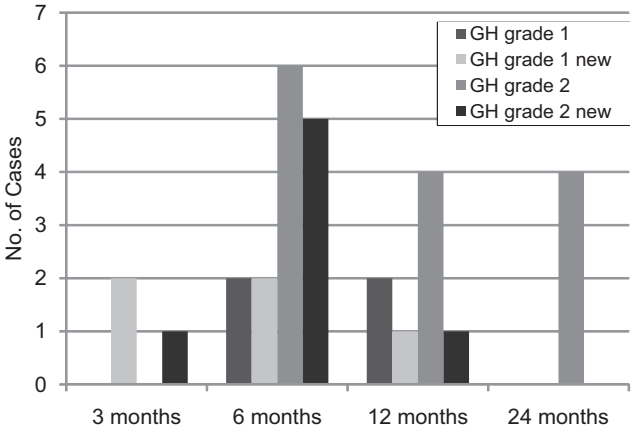

Figure 3. Occurrence of graft hypertrophy (GH). The GH occurred during the first 12 postoperative months. No new cases of GH could be observed in the follow-up examination after 24 months.

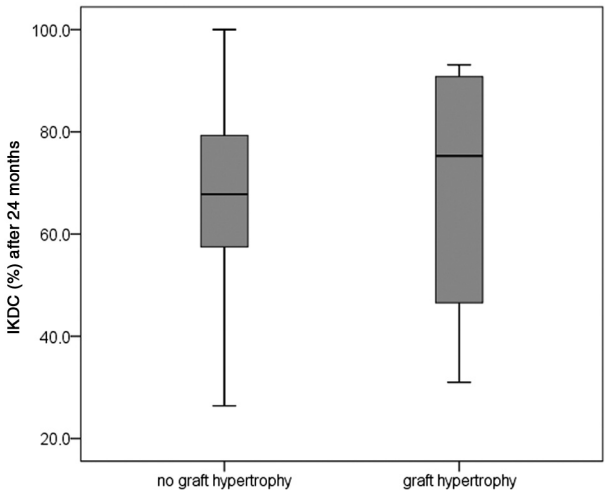

Figure 4. Clinical International Knee Documentation Committee (IKDC) results after 2 years in patients with graft hypertrophy grades 1 and 2. The difference between the clinical results (IKDC) is not statistically significant.

occurrence of GH using the mb-ACI method and its clinical relevance are still uncertain.

Up to now, GH after mb-ACI was only descriptively analyzed according to its macroscopic appearance in arthroscopy or in MRI examinations.[1,17] Therefore, a comparison between these observations and results of studies using different methods is either insufficient or not possible. Kreuz et al[12] were the first to establish a GH classification with the use of MRI examinations and classified the GH in 4 grades. This form of classification was only performed in the classic ACI using periosteal flap plastic, and therefore, no results existed for the GH after mb-ACI.

This study closes the gap by revealing data regarding the GH after mb-ACI and its influence on the clinical results. The thickness of the graft as well as the thickness of the adjacent healthy cartilage was determined by means

of postoperative MRI examinations at regular intervals, and its course was observed. The ratio between the thickness of the graft and the thickness of the healthy cartilage was determined and could now classify the GH. The standardized graft and healthy cartilage measurements were conducted by determining the mean values of 3 measuring points in the thickest region of the tissue. The MRI sequence for determining the cartilage thickness of the knee joint is an established method.[5-7]

The aim of this study was to analyze the occurrence of hypertrophic cartilage growth in the knee joint after mb-ACI and its postoperative course in 2 years. The following hypotheses could be answered:

- Hypertrophy as a complication after mb-ACI treatment of circumscribed cartilage defects occurs in 25%, as frequently as reported in classic p-ACI (9%-40%).[1,15,20]
- The occurrence of GH in the postoperative course after mb-ACI in the knee joint is evident after the first 12 months and in 75% of the cases within the first 6 months.
- Graft hypertrophy after mb-ACI treatment cannot be regarded as a complication because it does not lead to poorer clinical results in IKDC and VAS scores in a postoperative phase of 2 years. In our study, a second-look arthroscopy for the treatment of GH was not necessary.
- The patients in our collective showed significant improvement of the IKDC and VAS scores during the postoperative follow-up time span of 2 years. The improvement was significantly better compared with the preoperative results after 6, 12, and 24 months. A significant improvement of the IKDC score was evident between the 6th and 12th months. A positive, although insignificant, trend was observed between the 12th and 24th months.
- Graft hypertrophy after classic p-ACI was attributed to the periosteal flap. Based on this theory, a lower incidence of GH after mb-ACI would have been anticipated because a periosteal flap was not used, but this was not the case in this study. With a 25% incidence rate in our study, the rate of GH is similar to that of the classic p-ACI. One must therefore conclude that transplanted chondrocytes also have hypertrophy potential.[13] Nevertheless, we could not determine a correlation between the occurrence of GH and inferior clinical values in the IKDC or the VAS scores. It must therefore be clarified after which period of cartilage growth GH is to be considered a complication. The lack of GH grades 3 and 4 in our study supports the thesis that a temporary GH is to be regarded as an accommodation reaction and not a complication requiring treatment.

Graft Hypertrophy Occurs in the First 12 Months and Regresses in Most Cases Within 2 Years

Graft hypertrophy developed in 25% of the patients treated with mb-ACI within a postoperative course of 1 year. Sixteen percent of the patients developed hypertrophy grade 2, and 9% developed hypertrophy grade 1. These results are comparable to the frequency of occurrence of GH after classic p-ACI in the literature.[1,8,9] However, a direct comparison of the results from this study and the results from Kreuz et al[12] shows that the grades of GH are certainly lower and that no severe cases of GH such as grade 3 or 4 are observed. This explains why no patient in our study required revision surgery because of GH. All grade 1 GH cases in the series of Kreuz et al[12] did not require surgery as well. The lack of GH grades 3 and 4 in our examination supports the thesis that a temporary GH is more an accommodation reaction than a complication requiring treatment.

All the GHs in this study developed within 12 months postoperatively and in 75% of the cases within the first 6 months. A recurrence of GH in the second postoperative year could not be determined. All grade 1 GHs regressed within the second postoperative year. A progression to a grade 2 GH was observed in only one case. In patients who developed a grade 2 GH, the hypertrophy persisted within the 24-month postoperative phase without having a negative influence on the clinical outcome. In only 43% of the cases, a total regression after 2 years could be documented.

The majority of grade 1 GH cases can be considered "temporary" GH because these develop within the first year after implantation and are regressive in the course of the examination period. One can assume that the excessive growth of newly developing cartilage tissue comes to a standstill and even undergoes partial regression due to the biomechanical strain on it. After the development of grade 2 GH, a total adjustment of the new cartilage to the circumjacent level could be examined in less than 50% of the cases. Nevertheless, a correlation with this observation and poor clinical results could not be associated. In this case, with a persistence of the GH grade 2 after 24 months, it is possible that symptoms would arise.

Localization of Cartilage Damage Has No Influence on GH

There are contradictory propositions regarding classic p-ACI with periosteal flap and the occurrence of retropatellar GH in the literature.[2,12] In our study, a significantly higher occurrence of retropatellar GH could not be found. We rather saw the statistically insignificant tendency of more femoral GHs.

CONCLUSION

Matrix-based ACI does not lead to GH that requires treatment, as opposed to classic p-ACI of the knee joint. The frequency of occurrence of GH after p-ACI and mb-ACI is comparable. Nevertheless, with the mb-ACI method, only mild forms of GH classified as grades 1 and 2 were to be observed. Graft hypertrophy after mb-ACI occurs within the first postoperative year, and within the second year, all grade 1 GHs regenerated completely. This can therefore

be considered as a temporary excessive growth of regenerative cartilage tissue rather than a true GH. Grade 2 GHs persist in size in more than half of the cases after 2 years but do not progress. There was no negative influence of GH grades 1 and 2 on the clinical results in the IKDC and VAS pain scores during the 2-year postoperative time period. A correlation between the higher rate of GH to a certain localization of the grafts (femoral vs retropatellar) could not be verified. It seems that GH is therefore not a relevant complication in the treatment of circumscribed cartilage defects with mb-ACI.

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