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Classification of graft hypertrophy after autologous chondrocyte implantation of full-thickness chondral defects in the knee

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Summary

Objective: Graft hypertrophy is a major complication seen in autologous chondrocyte implantation (ACI) with a periosteal flap. We present the first magnetic resonance imaging (MRI) classification for periosteal hypertrophy including a grading of clinical symptoms and the surgical consequences.

Methods: One hundred and two patients with isolated chondral defects underwent an ACI covered with periosteum and were evaluated preoperatively, 6, 18 and 36 months after surgery. Exclusion criteria were meniscal pathologies, axial malpositioning and ligament instabilities. Baseline clinical scores were compared with follow-up data by paired Wilcoxon-tests for the modified Cincinnati knee, the ICRS (International Cartilage Repair Society) and a new MRI score including the parameters defect filling, subchondral edema, effusion, cartilage signal and graft hypertrophy. Hypertrophic changes were graded from 1 (minimal) to 4 (severe).

Results: All scores showed significant improvement ($P < 0.001$) over the entire study period. Patients with femoral lesions had significantly better results than patients with patella lesions after 18 and 36 months postoperative ($P < 0.03$). Periosteal hypertrophy occurred in 28% of all patients. Fifty percent of all patella implants developed hypertrophic changes. No patient with grade 1, and all patients with grade 4 hypertrophy had to undergo revision surgery. The Pearson correlation between graft hypertrophy and ICRS score was 0.78 after 6 months, and 0.69 after 36 months ($P < 0.01$). Inclusion of graft hypertrophy in the MRI score improves the correlation to clinical scores from 0.6 to 0.69.

Conclusions: Grading graft hypertrophy helps to identify patients needing an early shaving of the graft. Its integration into an MRI score improves correlation with clinical scores. Re-operation depends on the grade of hypertrophy and clinical symptoms.

Key words: Autologous chondrocyte implantation, Periosteum, Classification, Scores.

Introduction

Hyaline cartilage has a limited capacity for intrinsic repair[1–3]. Efficacious treatment of chondral defects in the weight-bearing zone of the knee remains a challenging therapeutic problem[4]. To date, various articular cartilage-resurfacing techniques have the potential to improve the repair of cartilage defects and reduce the patient's disability. From all marrow stimulation techniques including microfracturing[5–9], abrasion chondroplasty[10] and drilling[11], the microfracture procedure has the greatest potential to provide good clinical long-term results[7–9]. Clinical studies have shown a significant superiority of microfracturing, osteochondral transplantation as well as autologous chondrocyte implantation (ACI) over debridement in the treatment of full-thickness chondral defects[8,12–15]. However, up today no surgical technique has so far been able to produce normal hyaline cartilage. Furthermore, there has been no randomized controlled prospective clinical trial that has proven significantly better results of ACI over mosaicplasty or microfracturing[16,17]. Knutsen *et al.* were the first investigators to compare the histological results after microfracture and ACI in human beings. There was a tendency for the ACI group to have more hyaline repair cartilage than the group undergoing the microfracture procedure, but this was not significant with the low number of patients available[5]. Osteochondral autografts require converting a chondral into an osteochondral injury to effect articular repair[14,15,18]. This may affect the ultimate function of the

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bone cartilage functional unit, including bonding problems with persistent interface between the transplant and the surrounding original cartilage[19]. In this context, Bentley *et al.*[20] reported in a prospective randomized clinical trial of ACI vs mosaicplasty a significant superiority of ACI at 1 year, but only in a *post hoc* subgroup analysis of participants with medial condylar defects. The conclusions are still controversial since other studies found equally good results with both surgical techniques[19,21].

Nevertheless ACI has been established as an effective treatment for large chondral defects in the knee. Until now good long-term results over 10 years have been described only with the periosteum covered ACI which was introduced by Peterson in 1987[22–25]. The most common problem after the classic ACI procedure is a periosteal hypertrophy described as being up to 36% in the literature[26–31]. Until now, no classification has been available. The present prospective study presents a novel magnetic resonance imaging (MRI) classification for periosteal hypertrophy including a grading of clinical symptoms and the surgical consequences.

Patients and methods

INCLUSION AND EXCLUSION CRITERIA

Between 1996 and 2000, a total of 102 patients (63 male and 39 female) with isolated chondral lesions of the knee underwent an ACI combined with a periosteal graft (Figs. 1 and 2). The average patient age was 34 (range 18–50) years and average body mass index was 23.6 ± 2.6 (range 18–30) kg/m^2. All chondral defects were Outerbridge grade 3 or 4 lesions with an average size of 6.42 ± 3.05 cm^2 (range 3–16 cm^2) (Table I).

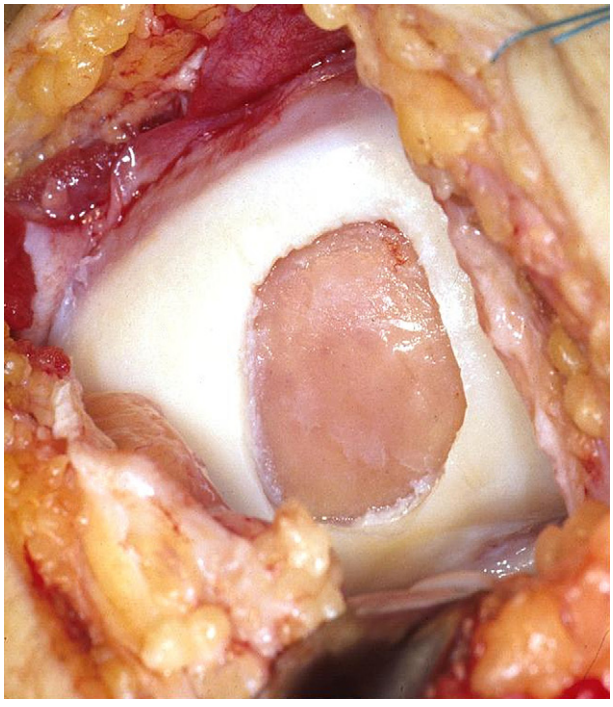

Fig. 1. Chondral defect on the medial femoral condyle measuring 5×3.5 cm. The prepared lesion has a stable perpendicular edge of healthy, well-attached viable cartilage surrounding the defect providing a pool to hold the chondrocyte suspension within the defect area.

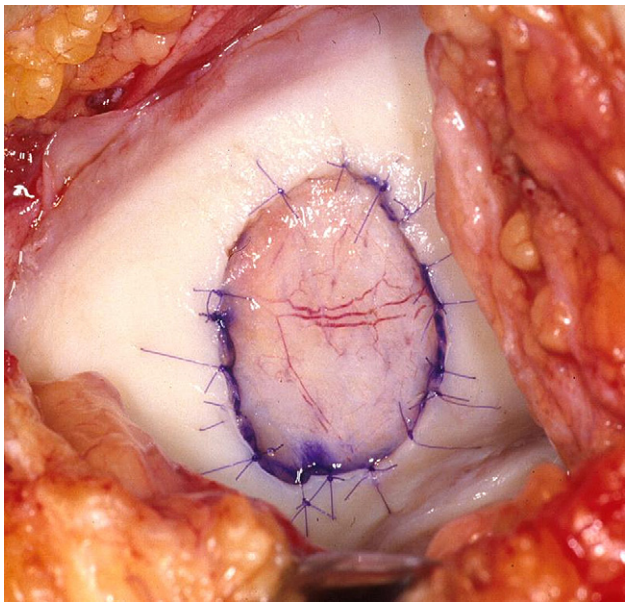

Fig. 2. ACI with a periosteal cover. The flap is sutured to the surrounding rim of the prepared defect area to create a water-tight chamber.

Excluded were patients with acute trauma, varus or valgus deformities with a malalignment over 5°, limits in knee extension or flexion less than 130°, patella-malalignment with a medial or lateral shift of more than 0.5 cm, instabilities of the collateral or cruciate ligaments, meniscal pathologies, osteochondral defects, intra-articular corticosteroid injections within the previous month or knee arthroscopy within the previous 6 months. Varus or valgus deformities could be excluded by X-ray of the whole leg, and the correct patella position was detected by a routine medio-lateral, femoro-patellar and axial joint radiograph.

PATIENT EVALUATION AND SCORES

All patients were evaluated preoperatively and 6, 18 and 36 months postoperatively using two clinical and one MRI scores: the modified Cincinnati score[32], the ICRS scoring-system[33], and the Henderson MRI classification with the following criteria: defect filling (1 = complete; 2 ≥ 50% of the defect; 3 < 50% and 4 = full-thickness defect), cartilage signal (1 = normal, i.e., identical to the adjacent articular cartilage; 2 = nearly normal, i.e., slight areas of hyperintensity; 3 = abnormal, i.e., larger areas of hyperintensity; and 4 = absent), subchondral edema and effusion (both graded as 1 = absent; 2 = mild; 3 = moderate; and 4 = severe) [Figs. 3 and 4(a)][34]. However hypertrophic changes of the graft are not considered in this classification. Thus we added a fifth criterium, namely "graft hypertrophy" [Table II; Figs. 4(a–e) and 5]. Additionally, we assigned an overall MRI score, corresponding to the worst score in the five categories. The details of the score are listed in Table II. All MRIs were evaluated by two experienced radiologists.

MRI

All patients were investigated in a state of the art 1.5 T-MRI scanner (Sonata®, Siemens, Erlangen, Germany),

Table I
Preoperative patient information: the parameters defect size, defect grade, body mass index and preoperative scores were not significantly different between the three groups (P > 0.1, Mann–Whitney U test). This makes the groups comparable

Group (1–3)	Total	1: Femoral condyles	2: Trochlea	3: Patella
Number of patients	102	75	9	18
Gender (male:female)	63:39	53:22	5:4	5:13
Body mass index in kg/m^2 (range)	23.6 ± 2.6 (18–30)	23.7 ± 2.5 (18–30)	23.8 ± 2.1 (21–27)	23.3 ± 3.2 (18–30)
Side (right:left)	58:44	46:29	4:5	8:10
Outerbridge classification (range)	3.95 ± 0.22 (3–4)	3.96 ± 0.20 (3–4)	3.89 ± 0.33 (3–4)	3.94 ± 0.24 (3–4)
Defect size in cm^2 (range)	6.42 ± 3.05 (3–16)	6.57 ± 2.98 (3–16)	6.7 ± 4.1 (3–13)	5.7 ± 2.8 (3–12)
Average age in years (range)	34.0 ± 8.8 (18–50)	35.3 ± 8.7 (18–50)	34.0 ± 5.1 (28–42)	28.4 ± 8.8 (18–43)
Preoperative scoring				
1. ICRS score	3.78 ± 0.41	3.81 ± 0.39	3.67 ± 0.5	3.72 ± 0.46
2. Cincinnati score	3.58 ± 0.49	3.56 ± 0.49	3.56 ± 0.53	3.67 ± 0.49

using a standard flexible knee-coil and following MRI-sequences:

T2-weighted fat-saturated (fs) coronal fast spin echo-sequence (FSE) [repetition time (TR) 4540 ms, echo time (TE) 26 ms, matrix 416 × 512 pixel).
T1-weighted spin-echo-sequence (SE) (TR 715 ms, TE 20 ms, matrix 416 × 512 pixel).
Proton-density-weighted sagittal SE-sequence (TR 2580 ms, TR 31 ms, matrix 636 × 768 pixel).
T2*-weighted fs sagittal gradient-echo-sequence (DESS (dual echo at steady-state); TR 22.5 ms, TE 6.06 ms, flip angle 20°, matrix 448 × 512 pixel). Field-of-view was 87 × 87 mm in all sequences. Slice thickness of all mentioned sequences was 3 mm with exception of the gradient-echo-sequence (1 mm). The duration of the whole MRI-investigation was about 20 min.

Validity tests in the determination of knee-joint cartilage thickness and hypertrophy by using MRI were performed by the working group of Eckstein *et al.*[35–37]. In their investigations MRI was carried out at 1.5 T with 3D-Flash and 3D-Dess sequences as used in our study protocol. Images were performed in cadaveric knee-joint specimens and volunteers. Following imaging, anatomical sections were obtained at intervals of 2 mm with a diamond band saw. Cartilage volumes and topographical thickness maps were obtained and compared with those derived by image analysis. The deviations of the MR volumes from those of the sections were only 4.7% in the patella, 3.1% in the tibia plateau and 4.2% in the femur. The intraobserver and interobserver reproducibilities were very high in both the specimens and the volunteers, showing that the thickness and volumes of knee-joint cartilage may be accurately determined with MRI.

Fig. 3. Control arthroscopy 12 months after ACI in a 38-year-old man. The defect is completely filled without any fissures or signs of hypertrophy.

ACI

The ACI procedure was performed in two stages as described by Peterson and Brittberg (Figs. 1 and 2)[22,24,25]. Cell cultures were performed at Metreon Bioproduct GmbH, a subsidiary of CellGenix Technology Transfer GmbH, Freiburg, Germany. The periosteal graft was harvested from the proximal tibia[38].

REHABILITATION

After the surgical procedure, the leg was enclosed in a compressive bandage, rested, and elevated for 12 h to avoid detachment of the membrane. After 12 h, continuous passive motion was started for 6–8 h per day[39].

Cold therapy was used for all patients for 1 week. Crutch-assisted touchdown weight-bearing was performed for 6 weeks after the surgical procedure. Afterwards the patients progressed to full weight-bearing and began a more vigorous program of active motion of the knee. Crutch free walking was permitted after 3 months, and return to sports was permitted after 4–6 months depending on the clinical examination.

STATISTICAL ANALYSIS

Baseline clinical scores were compared with follow-up data by paired Wilcoxon-tests and Friedman-tests for the modified Cincinnati knee score[32] and the ICRS score[33]. Statistical comparison of different groups was performed using the Mann–Whitney *U* test for non-parametric data[40]. Furthermore, MRI characteristics and clinical scores were compared using the Pearson coefficient of correlation. All statistics were performed with SPSS (version 11.0) and reviewed by an independent statistician. A *P*-value < 0.05 was considered statistically significant.

Results

Seventy-five defects were located on the femoral condyles (group 1), nine on the trochlea (group 2) and 18 on the patella (group 3). There was no significant difference

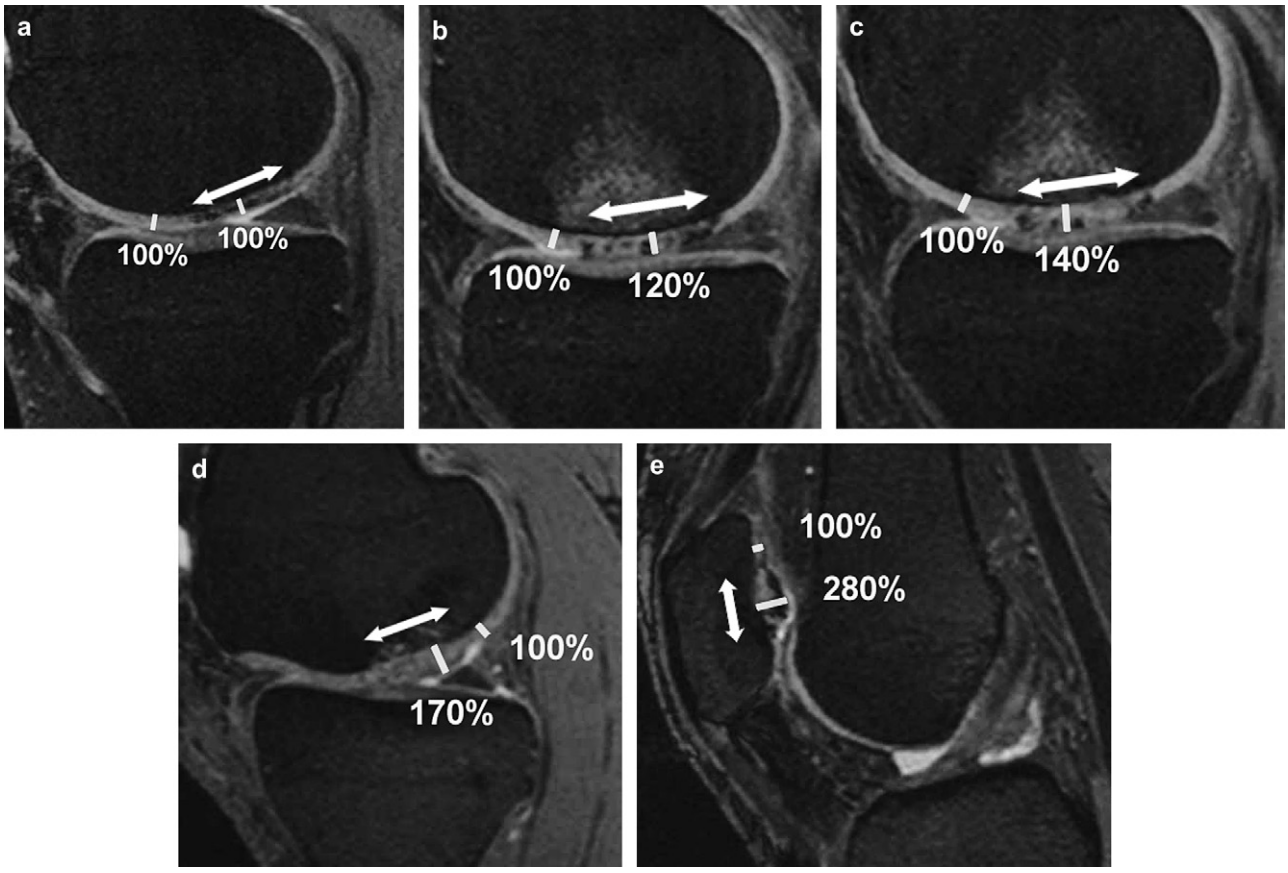

Fig. 4. Grading of graft hypertrophy: sagittal T2*-weighted, fat-suppressed gradient-echo-sequences of different grades of hypertrophy. The area of ACI is marked in every MR image with a white arrow. The thickness of the tissue graft is marked with a white bar. As reference value serves the thickness of the surrounding cartilage. It is marked with a white bar as well and set 100%. (a) No hypertrophy: the defect is completely filled without signs of subchondral edema and well integrated in the adjacent cartilage. (b) Grade 1 hypertrophy (≤125%): minimal hypertrophic changes of the graft without any symptoms. (c) Grade 2 hypertrophy (≤150%): mild hypertrophy of 140% compared to the surrounding articular cartilage. (d) Grade 3 hypertrophy (≤200%): moderate hypertrophy of 170% with symptoms of blocking and need for arthroscopic trimming. (e) Grade 4 hypertrophy (>200%): the transplanted area shows a severe graft hypertrophy of 270% with patellar pain and need for a surgical intervention.

($P > 0.1$) regarding defect size, defect grade, body mass index and preoperative scores among the three groups (Table I). This makes the groups comparable.

Before surgery all patients were evaluated "poor" or "fair" with the modified Cincinnati score and "abnormal" or "severely abnormal" using the ICRS classification system.

The scores improved significantly in all three groups over the entire study period, between preoperative and 6 months, and between 6 and 18 months postoperative ($P < 0.01$). In trochlear and retropatellar defects we noted no further improvement between 18 and 36 months postoperative ($P > 0.1$) (Table III). Significantly better results were detected in both scores after 18 and 36 months in femoral (1) compared to retropatellar (3) defects ($P < 0.03$) (Table IV).

The Pearson coefficient of correlation between both scores (overall) was 0.7 after 6 months, 0.69 after 18 months, and 0.76 after 36 months. Regarding the entire study period, the Cincinnati score rose by 1.66 and the ICRS score by 1.59 points with no significant difference between the two scores (Table III).

Table II
MRI classification including the parameter graft hypertrophy. The overall MRI score corresponds to the worst score in the five categories

Defect filling	Graft hypertrophy	Cartilage signal	Subchondral edema	Effusion	Overall MRI score
1 = Complete	1 = Minimal (≤125%)	1 = Normal (identical to adjacent cartilage)	1 = Absent	1 = Absent	1 = Excellent 2 = Good
2 ≥ 50% of the defect	2 = Mild (≤150%)	2 = Nearly normal (slight areas of hyperintensity)	2 = Mild	2 = Mild	3 = Fair 4 = Poor
3 < 50% of the defect	3 = Moderate (≤200%)	3 = Abnormal (larger areas of hyperintensity)	3 = Moderate	3 = Moderate	
4 = Full-thickness defect	4 = Severe (>200%)	4 = Absent	4 = Severe	4 = Severe	

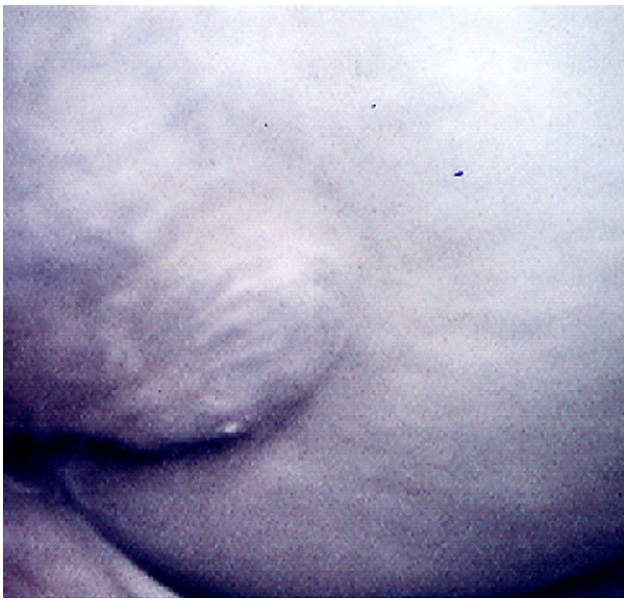

Fig. 5. Control arthroscopy 6 months after ACI in a 33-year-old man. The defect is filled with well integrated but extensive hypertrophic repair tissue responsible for clinical symptoms such as blocking, effusion and pain. The hypertrophic area was trimmed down with a shaver to the level of the surrounding cartilage.

MRI

Control MRIs after 6 months revealed periosteal hypertrophy in 28% of all patients [Table V(a); Figs. 4(b–e) and 5], of whom only two were ≥40 years. Fifty percent of all patients with an ACI on the patella developed graft hypertrophy. Scoring after 6 months revealed no clinical symptoms in grade 1 hypertrophic changes [Fig. 4(b)]. There was no significant difference in the clinical scores between patients with no and grade 1 hypertrophy ($P > 0.05$). However, both clinical scores deteriorated from grade 1 to 4. A re-operation was necessary in 50% (eight patients) of grade 3 periosteal hypertrophies [Table V(a) and Fig. 4(d)]. Thereof six cases could be controlled by arthroscopic shaving. In two patients gaps were detected between the reparative tissue and the surrounding cartilage. The hypertrophic area was trimmed down with an arthroscopic rotatory blade and microfracture was performed in the region without integration to the surrounding cartilage. In contrast to grade 3 hypertrophic changes surgical intervention was necessary in 100% (four patients) of grade 4 periosteal hypertrophies [Table V(a) and Fig. 4(e)]. In two patients the reparative tissue could be controlled by arthroscopic shaving. In two other patients the newly formed tissue was soft and impressible with fissures and missing integration. Therefore we decided to perform a second ACI. Overall 28% of all patients with hypertrophic changes had to undergo surgery again. After 36 months grade 3 and 4 changes were no longer detectable (Table V(b)). No patient with grade 1 or grade 2 hypertrophy had to undergo a further surgical intervention. After 36 months the ICRS and Cincinnati score had increased significantly more in all patients without re-operation ($2.17 \pm 0.66/1.87 \pm 0.66$ points) compared to $2.5 \pm 0.76/2.38 \pm 0.92$ points in the eight patients that were re-operated for graft hypertrophy in the first year after ACI ($P = 0.048$).

All five MRI parameters and the overall MRI score improved significantly from 6 to 36 months postoperative ($P < 0.05$) (Table VI). Patients < 40 years showed significantly better results than patients ≥ 40 years ($P < 0.01$).

The Pearson correlation between clinical scores and the parameter defect filling (without grading graft hypertrophy) was only ≤0.39, as opposed to ≥0.65 with a 2-parameter MRI score including graft hypertrophy and defect filling (Table VII).

Furthermore, the correlation between clinical scores and our 5-parameter MRI score (Table II) is 0.69 6 months after surgery compared to 0.6 with a 4-parameter MRI score without graft hypertrophy. No further difference was detectable after 36 months (Table VII).

Discussion

Periosteum is able to promote cartilage formation in a chondrotrophic environment[41,42]. Free periosteal grafts transplanted to chondrectomized articular surfaces of different joints in experimental animals differentiated into a mixture of fibrous tissue and fibrocartilage[43–46]. This chondrogenic potential arises because the cambium layer of periosteum contains growth factors and chondrocyte precursor cells that form cartilage during limb development, and does so once again during fracture healing or periosteum transplantation. The regenerative capacity is determined by surgical factors such as orientation of the cambium layer, postoperative factors such as the use of continuous passive motion, and the age and maturity of the experimental animal[41,42].

Table III

ICRS and Cincinnati scores preoperative and 6,18 and 36 months after ACI in different defect locations (1–3). The scores improved significantly in all three groups (P < 0.05) over the entire study period, between preoperative and 6 months and between 6 and 18 months postoperative. There was no more improvement in trochlear (2) and retropatellar (3) defects between 18 and 36 months postoperative (P > 0.1)

Group	1	2	3	Overall
Average ICRS score				
Preoperative	3.81 ± 0.39	3.67 ± 0.5	3.72 ± 0.46	3.78 ± 0.41
After 6 months	2.81 ± 0.67	2.89 ± 0.6	2.83 ± 0.62	2.82 ± 0.65
After 18 months	2.24 ± 0.61	2.44 ± 0.53	2.56 ± 0.51	2.31 ± 0.59
After 36 months	2.12 ± 0.67	2.22 ± 0.67	2.5 ± 0.62	2.19 ± 0.67
Average Cincinnati score				
Preoperative	3.56 ± 0.49	3.56 ± 0.53	3.67 ± 0.49	3.58 ± 0.49
After 6 months	2.4 ± 0.64	2.44 ± 0.53	2.56 ± 0.51	2.43 ± 0.61
After 18 months	1.91 ± 0.64	2.11 ± 0.78	2.22 ± 0.65	1.99 ± 0.65
After 36 months	1.84 ± 0.68	2.0 ± 0.71	2.22 ± 0.65	1.92 ± 0.68

Defect location – 1: femoral condyles; 2: trochlea; 3: retropatellar.

Table IV

Results on the defect location: listed is always the P*-value (Mann–Whitney* U *test for independent samples) between the scores of two different defect locations. Significantly better results were detected after 18 and 36 months in femoral (1) compared to retropatellar (3) defects in both scores (*P < 0.03)*

Time after ACT	6 Months postoperative		18 Months postoperative		36 Months postoperative	
Score	ICRS	Cincinnati	ICRS	Cincinnati	ICRS	Cincinnati
Location 1–2	$P = 0.7$	$P = 0.79$	$P = 0.27$	$P = 0.33$	$P = 0.59$	$P = 0.44$
Location 1–3	$P = 0.86$	$P = 0.26$	$^*P = 0.027$	$^*P = 0.013$	$^*P = 0.019$	$^*P = 0.017$
Location 2–3	$P = 0.86$	$P = 0.67$	$P = 0.67$	$P = 0.67$	$P = 0.28$	$P = 0.42$

Defect location – 1: femoral condyles; 2: trochlea; 3: retropatellar. *Mann–Whitney U test with $P < 0.03$.

Hypertrophic changes are one of the most common adverse events in ACI using a periosteal graft[27,29,31,47]. Biopsy specimens have shown that the most superficial layer of the regenerative tissue is composed of fibrocytes and sparse matrix, which most likely represents incorporated metaplastic periosteal remnants[25]. The role of growth factors such as vascular endothelial growth factor (VEGF) in the development of hypertrophic tissue formation is still unclear. However, animal studies have shown that periosteal cells in the grafted tissue differentiate into chondrocytes to form cartilage[48]. Some chondrocytes are immunopositive for VEGF expression. This process could play an important role not only for hypertrophic changes but also for blood vessel invasion and endochondral ossification, which can be seen sometimes on the base of the repair tissue[48]. However, the present study revealed no correlation between graft hypertrophy and periosteum taken from macroscopically well-vascularized areas (Fig. 2). Furthermore, we tried to prepare the periosteal patch as thin as possible removing all attached adipose tissue to reduce all factors that might influence or stimulate tissue hypertrophy.

Scoring after 6 months revealed no clinical symptoms in grade 1 hypertrophic changes [Fig. 4(b)]. There was no significant difference in the scores of patients with no and grade 1 hypertrophy ($P > 0.05$). Therefore we gave 1 point to patients with grade 1 hypertrophy in the MRI score, the same score-value as in patients with complete defect filling.

A surgical intervention was necessary in 50% of grade 3 [Fig. 4(d)], and in 100% of grade 4 [Fig. 4(e)] periosteal hypertrophies. Grade 3 and 4 changes were no longer detectable after 36 months and the number of patients with grade 2 hypertrophies had fallen from 11 to 5. This means that minimal grade 1 and 2 hypertrophic changes may diminish over the time without surgical intervention. That is probably a result of compression and tissue remodeling during normal joint motion and weight bearing. However, we observed that hypertrophic changes >200% were always associated with severe clinical symptoms ($P < 0.001$) and need for a surgical intervention [Figs. 4(e) and 5]. The incidence of graft hypertrophy after ACI was as follows in our study population: 50% on the patella, 25.3% on the femoral condyles, and 11.1% on the trochlea. Others have reported that patellar lesions do not fare as well as condylar lesions[22], thus attention to correction of patellofemoral maltracking has been emphasized as a means of improving outcome[25]. Since maltracking was excluded in our study population, we postulate that there is another explanation for patellar lesions' worse results. Six of the nine treated patellar chondral defects were located on the medial patellar facet. However, this area has often no direct contact to the opposite trochlea

Table V

Grading of periosteal hypertrophy 6 (a) and 36 (b) months postoperative: 29 of all patients showed hypertrophic changes after 6 months. Only two of them were ≥40 years. Fifty percent of all patients with an ACI on the patella developed a graft hypertrophy. Scores after 6 months revealed no clinical symptoms in grade 1 hypertrophic changes. A surgical intervention was necessary in 50% of grade 3 and in 100% of grade 4 periosteal hypertrophies. After 36 months grade 3 and 4 changes were no longer detectable

Grade of graft hypertrophy	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Overall hypertrophy (grade 1–4)
(a) MRI 6 months after surgery						
Definition	No hypertrophy	100–125%	125–150%	150–200%	>200%	>100%
Number of patients	73 (71.6%)	6 (5.9%)	11 (10.8%)	8 (7.8%)	4 (3.9%)	29 (28.4%)
Age						
<40 Years	45	6	11	7	3	27
≥40 Years	28	0	0	1	1	2
Location						
Femoral Condyles	56	5	7	4	3	19
Trochlea	8	0	0	1	0	1
Retropatellar	9	1	4	3	1	9
Average ICRS score	2.37 ± 0.49	2.0 ± 0	3.0 ± 0	3.25 ± 0.46	3.5 ± 0.58	2.93 ± 0.59
Average Cincinnati score	2.08 ± 0.49	2.0 ± 0	2.18 ± 0.4	2.75 ± 0.46	3.0 ± 0	2.41 ± 0.5
Surgical intervention for hypertrophy	0	0	0	4 (50%)	4 (100%)	8 (27.6%)
(b) MRI 36 months after surgery						
Number of patients	91 (89.2%)	6 (5.9%)	5 (4.9%)	0 (0%)	0 (0%)	11 (10.8%)
Average ICRS score	1.91 ± 0.5	2.43 ± 0.53	3.0 ± 0	0	0	2.64 ± 0.5
Average Cincinnati score	1.65 ± 0.48	2.0 ± 0	2.75 ± 0.5	0	0	2.27 ± 0.47

Table VI

MRI 6 and 36 months postoperative: all MRI parameters and the overall MRI score improved significantly from 6 to 36 months postoperative ($P < 0.05$). The Mann–Whitney U test revealed in all parameters significantly better results in patients < 40 years compared to patients ≥ 40 years ($P < 0.01$)

MRI parameter	Defect filling	Graft hypertrophy	Cartilage signal	Subchondral edema	Effusion	Overall MRI score (with hypertrophy classification)
6 Months after surgery						
Overall	1.62 ± 0.72	2.34 ± 0.97	1.81 ± 0.59	2.18 ± 0.62	1.45 ± 0.56	2.41 ± 0.68
Age < 40 years	1.29 ± 0.5	2.26 ± 0.94	1.6 ± 0.56	1.9 ± 0.61	1.4 ± 0.5	2.27 ± 0.74
Age ≥ 40 years	2.14 ± 0.71	3.5 ± 0.71	2.17 ± 0.59	2.53 ± 0.63	1.57 ± 0.62	2.7 ± 0.65
36 Months after surgery						
Overall	1.23 ± 0.49	1.36 ± 0.5	1.33 ± 0.51	1.31 ± 0.51	1.17 ± 0.4	1.34 ± 0.54
Age < 40 years	1.1 ± 0.33	1.3 ± 0.48	1.1 ± 0.31	1.1 ± 0.31	1.1 ± 0.18	1.13 ± 0.35
Age ≥ 40 years	1.52 ± 0.69	2.0 ± 0.0	1.73 ± 0.58	1.7 ± 0.6	1.37 ± 0.56	1.73 ± 0.64

which should give a kind of containment for the transplanted area. This missing contact to the trochlea could be a reason for the unhampered growth of the periosteal graft after ACI on the medial patellar facet. The high number of patients with hypertrophic changes on the patella may have led to the significantly better results of femoral (1) compared to patellar (3) lesions after 18 and 36 months ($P < 0.03$) (Table IV).

Twenty-seven of all 29 patients with hypertrophic changes were aged < 40 years. The low incidence of graft hypertrophy in older patients may be due to a diminished proliferative capacity of the periosteal flap's cambium layer. Animal studies have shown that the chondrogenic potential of periosteum decreases with age[41,42,49]. The reduced regenerative capacity of chondrocytes could be a reason for the worse results of patients over 40 years compared to younger patients. Chondrocyte senescence is associated with a decline in mitochondrial function, synthetic and mitotic activity and with a decreased responsiveness to anabolic mechanical stimuli and growth factors[50,51]. In this context, MRIs have shown a significantly worse defect filling in patients over 40 years. Glaser and Putz[52] have analyzed articular cartilage under compressive loading by scanning-electron-microscopy. They showed, that the removal of the upper tangential zone was associated with increased overall superficial tangential strain and high peaks of surface tensile strain, leading to fissures. This could be an additional reason for the worse results and the higher number of inhomogeneous cartilage signals and subchondral edemas of patients over 40 years (Table VI). In the present study we did not find a correlation between graft hypertrophy and subchondral edema. In grade 4 hypertrophic changes [Figs. 4(e) and 5] a severe subchondral edema was only detected in the two patients with a soft and impressible newly formed tissue with missing integration and need for a second ACI.

The importance of grading hypertrophy as part of an overall MRI score is obvious when one compares our MRI score with and without the graft-hypertrophy parameter (Table VII). When hypertrophic changes are disregarded, the Pearson correlation between clinical scores and defect filling is significantly reduced. Moreover, the correlation between clinical scores after 6 months and the overall MRI score not including the graft-hypertrophy parameter is worse ($P < 0.05$) than the overall MRI score including hypertrophic changes (Table VII). After 36 months, the Pearson correlation showed no more difference between the MRI score with and without grading hypertrophy (Table VII). This may be explained by the decline in hypertrophic changes from 28.4% after 6 months to 10.8% after 36 months, and the shift of patients with grade 3 and 4 to grade 0, 1 and 2 changes.

This study demonstrates that grading periosteal hypertrophy makes good clinical sense and should be incorporated into an overall MRI score for better correlation with clinical scores. Furthermore, grading identifies patients needing early arthroscopic shaving of the graft to avoid increased shear-stresses with risk of fissures and graft failure. Reoperation depends on the grade of hypertrophy and clinical symptoms.

Table VII

Pearson correlation between MRI and clinical scores: the parameters defect filling, graft hypertrophy, and cartilage signal correlated best with clinical scores after 6 and 36 months. The Pearson coefficient of correlation between clinical and MRI scores remained always ≥0.67 and was significant at the 0.01 level. The table compares the results of an MRI score with (*) and without (**) grading hypertrophy. Without grading hypertrophy, the Pearson correlation between clinical scores and defect filling drops to ≤0.39. Furthermore, the correlation between clinical scores and overall MRI score without grading hypertrophy is only 0.6, compared to 0.69 with an MRI score including hypertrophic changes

	Defect filling	Graft hypertrophy	Subchondral edema	Cartilage signal	Effusion	Overall MRI score
ICRS score, 6 months	0.77 (*) 0.35 (**)	0.78	0.52	0.81	0.61	0.69 (*) 0.6 (**)
Cincinnati score, 6 months	0.67 (*) 0.39 (**)	0.72	0.56	0.56	0.48	0.69 (*) 0.6 (**)
ICRS score, 36 months	0.65 (*) 0.32 (**)	0.69	0.66	0.70	0.61	0.69 (*) 0.69 (**)
Cincinnati score, 36 months	0.65 (*) 0.39 (**)	0.67	0.65	0.70	0.59	0.67 (*) 0.67 (**)

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