Autologous Chondrocyte Implantation for Treatment of Cartilage Defects of the Knee

What Predicts the Need for Reintervention?

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Background: Autologous chondrocyte implantation (ACI) is a well-established treatment option for isolated cartilage defects of the knee joint, providing satisfying outcome. However, cases of treatment failure with the need for surgical reintervention are reported; typical patient’s individual and environmental risk factors have previously not been described.

Hypothesis: The need for reintervention after ACI is associated with specific preoperative detectable individual risk factors.

Study Design: Cohort study; Level of evidence, 3.

Methods: A total of 413 patients following ACI (first, second, and third generation) were filtered for those who required revision surgery during their follow-up time (2-11.8 years). Factors were analyzed that might have significant effects on increased revision rate. Using preoperatively collected data, all patients were grouped according to 12 standard prognostic factors. Apart from odds ratio and Pearson \( \chi^2 \) test, statistical analysis of risk factors was performed with multivariate binary logistic regression models and Cox regression, the method of choice for survival time data.

Results: After a follow-up of 4.4 ± 0.9 years (limited to 5 years), a total of 88 patients (21.3%) had undergone surgical revision. The time to revision surgery was 1.8 ± 1.1 years. Four prognostic factors associated with a significantly higher risk for reintervention were detected: (1) female gender (Cox survival fit: \( P = .033 \)), (2) previous surgeries of the affected joint (\( P = .002 \)), (3) previous bone marrow stimulation (\( P = .041 \)), and (4) periosteum patch-covered ACI (\( P = .028 \)). An influence of patient age, body mass index (BMI), defect number, defect size, lesion origin, lesion location, parallel treatment, or smoking on the risk for reintervention could not be observed.

Conclusion: The study identifies clear facts that significantly increase the risk of revision surgery. These facts can be easily obtained preoperatively and may be taken into consideration when indicating ACI.

Keywords: risk factors; outcome; autologous chondrocyte implantation; cartilage lesion; knee surgery

Autologous chondrocyte implantation (ACI) has become an accepted therapy for focal cartilage defects across the knee joint, where efficacy and long-term durability have been demonstrated. Nevertheless, failure rates of this tissue engineering application vary between 10% and 20%, and various factors have been identified that are associated with inferior clinical outcome after ACI. Risk factors can be generally divided into modifiable and nonmodifiable circumstances, which are given by the individual patient and the specific injury he or she is currently suffering from. Established prognostic nonmodifiable risk factors associated with an increased incidence of knee osteoarthritis are previous knee injury, previous knee surgery, family history of osteoarthritis, and age. Risk factors that can be categorized as modifiable risk factors for osteoarthritis are overweight, repetitive knee bending, and physical activity. Previously, it has been reported that the failure rate of ACI is increased after unspecific previous knee surgery or after previous cartilage defect–specific treatment such as microfracture. Evaluating clinical symptoms, currently, several other risk factors for inferior clinical outcome are discussed, with diverging results. The most frequently considered parameters are surgical technique, parallel surgery, cause of the defect, defect size, defect location, age, gender, and obesity.


However, there are no clear data on how these specific factors might increase the risk for revision surgery after ACI, although this outcome-evaluating parameter is of increasing interest.\textsuperscript{13,17,21,27,45} Typical findings during revision arthroscopy have been reported and published earlier.\textsuperscript{30} The present article investigates prognostic circumstances among a total of 413 patients who underwent ACI for focal cartilage defects of the knee joint. The purpose of this study was to assess factors that are associated with treatment failure, preoperatively detectable epidemiological risk factors, and time of failure after ACI for treatment of a cartilage defect of the knee joint in a large patient cohort.\textsuperscript{22,23,30} We hypothesized that clearly important factors that increase the risk for the need for reintervention can be isolated and verified by different statistical analyses.

MATERIALS AND METHODS

Patients and Indication

Between 1997 and 2010, more than 500 patients were treated with ACI for focal full-thickness cartilage defects (graded III and IV according to the International Cartilage Repair Society [ICRS] classification) of the knee joint in our department. For all patients, the indication was confirmed during an initial arthroscopic procedure of the affected knee joint. Here, adjacent cartilage, defect size, defect grade, and integrity of the corresponding joint surface were addressed and documented according to the recommendations given by the ICRS.\textsuperscript{6} Exclusion criteria for ACI were uncontained large defects of several joint regions, significant degenerative changes of the affected joint (Kellgren-Lawrence >2), presence of inflammatory joint disease, and metabolic or crystal disorders. Noncorrectable ligamentous instability or meniscal defects were additional contraindications. Mechanical femorotibial axis was corrected by high tibial osteotomy in a parallel surgery if 5° malalignment or more was present. Patient information was documented in the hospital's patient registration, in a checklist, and in a medical letter. Because the aim of the study was to evaluate factors that are associated with revision surgery, 413 patients with at least a 2-year follow-up after ACI and complete documentation at baseline were included in this study, of which 88 patients received reintervention for ACI at the same institution within a 5-year period. Necessary patient data of the reintervention time point were available for all 88 patients. Minimum follow-up was 2 years; maximum follow-up was 11.8 years.

Surgical Technique

During an initial arthroscopic procedure of the knee joint, which confirmed the indication, cells were harvested from the nonweightbearing or low-weightbearing articular cartilage at the intercondylar notch.\textsuperscript{31} Depending on the ACI technique, in vitro expansion was accomplished by either CellGenix (Freiburg, Germany) for cell suspensions (periosteum patch-covered ACI and Chondro-Gide-covered ACI) or BioTissue Technologies (Freiburg, Germany) for BioSeed-C (matrix associated) procedure. Expansion time was approximately 4 to 6 weeks. The second operative procedure was performed by 1 of 4 equally trained and experienced surgeons, using an arthroscopy of the knee joint. The cartilage defect area was debrided until its edges were completely surrounded by healthy cartilage. Care was taken to debride the cartilage entirely with a curette and a scalpel. The calcified layer was preserved. The size of the lesion was measured (in mm) and the treated area calculated (in mm$^2$). Documentation was again performed according to ICRS recommendations.\textsuperscript{30}

For periosteum patch-covered ACI (109 patients), the periosteal patch was harvested from the proximal tibia via an additional incision during the same surgery.\textsuperscript{5} The initial chondrocyte cell pellet of 1 mL was adequately diluted to the necessary volume for the specific lesion. This suspension was injected below the periosteum layer. The periosteum flap was fixated in a circular manner with polydioxanone suture material (6-0, Ethicon Inc, Johnson & Johnson, Nordersted, Germany). In those cases where the Chondro-Gide membrane (Geistlich, Wolhusen, Switzerland) (235 patients) was used, it was cut to size,\textsuperscript{23} and expanded chondrocytes were applied using a porcine type I/III collagen membrane (Chondro-Gide)\textsuperscript{16,44} Afterward, the membrane was placed above the defect and sutured as described above. Then, the transplant was sealed with fibrin glue (Tissucol, Baxter GmbH, Heidelberg, Germany). For the matrix-associated ACI (BioSeed-C) (69 patients), the matrix consisted of cells cultured on a 3-dimensional poly(lactic-co-glycolic) acid fleece, which was implanted using a transosseous fixation technique.\textsuperscript{11} After the transplant had been fixed, a drain was placed intra-articular, and the wound was closed in layers.

Concerning the postoperative procedure, weightbearing was limited to 15 kg on the affected side for the initial 6 weeks. Afterward, weightbearing load was gradually increased to reach full weightbearing after 8 to 12 weeks. Additionally, flexion was limited to 30° for the first 2 weeks and then to 60° for the following 2 weeks to reduce retropatellar pressure. The use of continuous passive motion (CPM, Ormed-DJO, Freiburg, Germany) as well as physiotherapy with isometric exercises designed to strengthen the joint were continued during follow-up.

Indication for Reintervention

Need for revision surgery represents a well-established parameter that has been used by many authors in similar studies that evaluate risk factors for failure of various therapies, analyzing large patient cohorts.\textsuperscript{7,13,21,27,28} Indication for revision surgery was made in every case individually following close communication between the patient and the treating physician, who generally had previously performed the ACI. Revision surgery was carried out when either one of the following persistent or recurrent symptoms or their combination strongly impaired the patient and was identified by the treating physician to be an indication for revision surgery:
grade drilling, autologous spongiosa grafts, or osteochondral transplants.

or cysts of the underlying bone were treated with ante-

age received a further ACI. Patients with osteonecrosis

procedure. Moreover, 2 patients with traumatic ACI dam-

with debridement or abrasion of loose regenerative carti-

joint, independent of the ACI, such as a traumatic menis-

fissuring. It consisted of debridement or of an additional

was dependent on the applied ACI technique (Table 1).

for persisting symptoms and for the need for reinterven-

treatment: yes and no; (10) previous surgery: no, one,

medial femoral condyle (MFC), lateral femoral condyle

location: multiple locations, found of the patella (patella),

traumatic-degenerative (PTD), and osteochondritis dissec-

number: one and multiple (either in the same or different

knee compartment); (4) defect size (cm

2

): <3 cm

2

; (5) origin: traumatic, degenerative, protracted

traumatic-degenerative (PTD), and osteochondritis dissec-

cans (OD)/flake fracture; (6) gender: male and female; (7)

location: multiple locations, found of the patella (patella),

medial femoral condyle (MFC), lateral femoral condyle
(LFC), and trochlea; (8) nicotine: yes and no; (9) parallel

treatment: yes and no; (10) previous surgery: no, one,

and multiple; (11) previous treatment: no, previous trans-

plantation, previous bone marrow stimulation (BMS), and

other; (12) technique: periosteum-covered ACI,

Chondro-Gide—covered ACI, and BioSeed-C.

Defects related to a trauma within the past 6 months

before surgical treatment were considered “traumatic,”

while those associated with a traumatic incident more

than 6 months before surgical treatment were considered

“posttraumatic.” For both origins, the most frequently

reported traumatic causes were sports injuries in soccer,

skiing, basketball, handball, climbing, surfing, tennis, or

 triple jump, as well as patellar luxation and non-sports-

related knee distortion. “Degenerative” defects were con-

sidered those cases in which no trauma could be evaluated.

Patients reporting previous OD or flake fracture mostly

received surgery in addition to ACI, either before or during

ACI treatment like implantation of an autologous spon-
giosa graft, Pridie drilling, or osteochondral refixation

(Table 2). Parallel treatments, defined as accompanying

surgical procedures during the same session, previous sur-

geries at the treated joint (presurgery), and previous treat-

ments of the cartilage defect (pretreatment), are presented

in the Appendix (available in the online version of this

article at http://ajs.sagepub.com/supplemental/). Patients

• the patient reported persistent pain at the operated

knee joint;

• the patient described significant loss of function of the

operated knee joint; and

• clinical findings and/or magnetic resonance imaging

(MRI) revealed compatibly pathologic changes to con-

firm each patient's symptoms, such as MRI evidence

of graft delamination, hypertrophy, severely abnor-

mal signal, insufficient fusion with adjacent cartilage,

or secondary transplant defects.

Indications for another operative procedure of the knee

joint, independent of the ACI, such as a traumatic menis-
cus rupture or cruciate ligament rupture, were not

included in the “reintervention” group but in the “no revi-
sion” group. The “reintervention group” was characterized

by an active manipulation at the transplantation site at

the time of revision surgery. During revision arthroscopy, 5

main final diagnoses, which were considered responsible

for persisting symptoms and for the need for reinterven-
tion, were identified. Frequency of the different diagnoses

was dependent on the applied ACI technique (Table 1).

(1) Treatment of transplant hypertrophy and arthrofibro-
sis consisted of debridement. (2) Insufficient fusion was

most frequently treated with additional adjunct micro-

fracture in the contact area. Different treatment was per-

formed for (3) insufficient/incomplete regenerative tissue

and (4) secondary ACI defects, including fibrillation and

fissuring. It consisted of debridement or of an additional

cartilage resurfacing procedure, such as revision ACI or

microfracture. (5) Cases with ACI delamination, commonly

associated with free intra-articular bodies, were treated

with debridement or abrasion of loose regenerative carti-

lage and excision of the free body in a following surgical

procedure. Moreover, 2 patients with traumatic ACI dam-

age received a further ACI. Patients with osteonecrosis

or cysts of the underlying bone were treated with ante-

grade drilling, autologous spongiosa grafts, or osteocon-

dral transplants.

Prognostic Factors

A total of 12 prognostic factors were categorized and ana-

lyzed in regard to their influence on the outcome of ACI

as follows: (1) age (years): <30, 30-39, and ≥40; (2) body

mass index (BMI; kg/m²): <25, 25-29, and ≥30; (3) defect

number: one and multiple (either in the same or different

knee compartment); (4) defect size (cm

2

): <3 cm

2

and

≥3 cm

2

; (5) origin: traumatic, degenerative, protracted

traumatic-degenerative (PTD), and osteochondritis dissec-

cans (OD)/flake fracture; (6) gender: male and female; (7)

location: multiple locations, found of the patella (patella),

medial femoral condyle (MFC), lateral femoral condyle
(LFC), and trochlea; (8) nicotine: yes and no; (9) parallel

treatment: yes and no; (10) previous surgery: no, one,

and multiple; (11) previous treatment: no, previous trans-

plantation, previous bone marrow stimulation (BMS), and

other; (12) technique: periosteum-covered ACI,

Chondro-Gide—covered ACI, and BioSeed-C.

TABLE 1

Number and Percentage of Arthroscopic Diagnoses at Revision Surgery

<table>
<thead>
<tr>
<th>Arthroscopic Diagnosis, n (%)</th>
<th>Total (N = 88)</th>
<th>Periosteum (n = 34)</th>
<th>Chondro-Gide (n = 43)</th>
<th>BioSeed-C (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete regenerative cartilage</td>
<td>25 (28.4)</td>
<td>6 (17.6)</td>
<td>17 (39.5)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Hypertrophy of transplant</td>
<td>20 (22.7)</td>
<td>17 (50)</td>
<td>1 (2.3)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Insufficient fusion with adjacent cartilage</td>
<td>14 (15.9)</td>
<td>4 (11.8)</td>
<td>8 (18.6)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Delamination of the transplant</td>
<td>17 (19.3)</td>
<td>7 (20.6)</td>
<td>9 (20.9)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Secondary ACI defect</td>
<td>11 (12.5)</td>
<td>5 (14.7)</td>
<td>5 (11.6)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Free Intra-articular body</td>
<td>8 (9.1)</td>
<td>5 (14.7)</td>
<td>3 (7.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adjacent cartilage defect</td>
<td>7 (8.0)</td>
<td>2 (5.9)</td>
<td>2 (4.7)</td>
<td>4 (36.6)</td>
</tr>
<tr>
<td>Arthrofibrosis</td>
<td>7 (8.0)</td>
<td>2 (5.9)</td>
<td>5 (11.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Soft regeneration tissue</td>
<td>6 (6.8)</td>
<td>1 (2.9)</td>
<td>3 (7.0)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>3 (3.4)</td>
<td>1 (2.9)</td>
<td>2 (4.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Subchondral cyst</td>
<td>2 (2.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (2.2)</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Five main causes for reintervention were identified, depending on their frequency on the applied surgical technique (periosteum patch-covered autologous chondrocyte implantation [ACI], Chondro-Gide-covered ACI, or BioSeed-C technique). Overall frequency is above 100% because of several patients presenting multiple diagnoses.

Indications for another operative procedure of the knee joint, independent of the ACI, such as a traumatic meniscus rupture or cruciate ligament rupture, were not included in the “reintervention” group but in the “no revision” group. The “reintervention group” was characterized by an active manipulation at the transplantation site at the time of revision surgery. During revision arthroscopy, 5 main final diagnoses, which were considered responsible for persisting symptoms and for the need for reintervention, were identified. Frequency of the different diagnoses was dependent on the applied ACI technique (Table 1).

(1) Treatment of transplant hypertrophy and arthrofibrosis consisted of debridement. (2) Insufficient fusion was most frequently treated with additional adjunct microfracture in the contact area. Different treatment was performed for (3) insufficient/incomplete regenerative tissue and (4) secondary ACI defects, including fibrillation and fissuring. It consisted of debridement or of an additional cartilage resurfacing procedure, such as revision ACI or microfracture. (5) Cases with ACI delamination, commonly associated with free intra-articular bodies, were treated with debridement or abrasion of loose regenerative cartilage and excision of the free body in a following surgical procedure. Moreover, 2 patients with traumatic ACI damage received a further ACI. Patients with osteonecrosis or cysts of the underlying bone were treated with antegrade drilling, autologous spongiosa grafts, or osteochondral transplants.
included in the “pretreatment” group represented a subgroup of the “presurgery” group. Within the group of patients in whom previous surgical interventions had been indicated, 124 patients had at least one previous cartilage treatment at the same location of the knee joint, mainly microfracture, Pridie drilling, or previous ACI. Several patients received multiple treatments; consequently, the overall number exceeds 100% for each parameter.

Statistical Analysis

IBM SPSS Statistics 18 (Chicago, Illinois) was used for statistical analysis designed to work up the data ascertained in this study. With the intention to measure dimension of the influence of every potential risk factor mentioned above on the therapy outcome, first the odds ratio \( \chi^2 \) test comparing with the particular control group and Pearson \( \chi^2 \) test were calculated. For further statistical evaluation of the factors, 2 different methods of statistical analysis were applied. Primarily, the effect of the risk factors was analyzed with a multivariate binary logistic regression model. The effects were tested using Wald tests. \( P \) values <.05 were considered statistically significant. Forward and backward regression models of multivariate binary logistic regression were used in comparison to confirm the results. In addition to standard binary logistic regression, in this work, Cox regression analysis using Kaplan-Meier curves (parametric survival fit) was performed to investigate simultaneously the influence of several factors on the time to event and correct for concomitant effects. Applying this method, differences in follow-up time were eliminated, which in particular are important for the parameter “surgical technique.” The primary end point was defined as date of reintervention or end of the observation period, respectively. Nearly two-thirds of patients had a follow-up of 5 years (62.5%). Therefore, we decided on a cutoff at a follow-up time point of 5 years to additionally adjust mean survival time for different surgical techniques. All patients without revision surgery within 5 years of follow-up were considered survivors. Three patients who received revision surgery later than 5 years after ACI were therefore also counted survivors. All \( P \) values are based on the likelihood ratio test and were considered significantly different when \( P < .05 \). To develop an even more stringent model, extracting only variables with an influence on the outcome, we used both forward and backward elimination (selection level \( P < .05 \)) in addition.

RESULTS

Complete baseline data of all 12 standard risk factors defined in this study were available for 413 patients (Table 3). Considering the follow-up as a Kaplan-Meier survival function (Figure 1), follow-up data for the fraction of individuals presenting for revision surgery during observation time were completely available without dropouts in this revision cohort \( n = 88 \). The Kaplan-Meier survival curve, presented as “failure curve” for the revision cohort, demonstrates an initial steep ascent of patients requiring reintervention, while reaching almost a plateau phase after 3.5 years (Figure 1). The follow-up time without reintervention in total was 6.0 ± 2.6 years; the follow-up time for first-generation ACI was 9.5 ± 1.8 years, for Chondro-Gide–covered ACI was 6.3 ± 1.0 years, and for BioSeed-C technique was 6.3 ± 1.0 years. The time to revision surgery was 1.7 ± 1.2 years for peristeme patch–covered ACI, 1.7 ± 1.1 years for Chondro-Gide–covered ACI, and 2.4 ± 1.2 years for BioSeed-C treatment, which were not significantly different. The overall time to reintervention was 1.8 ± 1.1 years. Follow-up was limited to 5 years to prevent different observation periods for different surgical techniques. After applying this 5-year follow-up restriction, the time of follow-up without reintervention was 4.4 ± 0.9 years. An overview of the analyzed potential risk factors including their specific incidence of patients with later need for reintervention for each category is given in Table 3. The age of the patients involved in the current study at the date of ACI was 34.9 ± 9.0 years; the BMI was 24.8 ± 3.5 kg/m² (height, 1.75 ± 0.1 m; weight, 76.2 ± 13.8 kg). The cartilage defect size was found to measure 5.6 ± 3.0 cm². The size of multiple transplants implanted during one operative session was cumulated for one knee. More than one transplant was necessary in 17.7% of the operative procedures. The highest disease incidence was found for the MFC, which was affected in 168 cases (40.7%), followed by patella lesions (26.7%). Isolated ACI for defects located on the trochlea (7.0%) or the LFC (9.0%) were less frequently observed. In a total of 68 patients, ACI was performed in more than one location of the knee joint. The origins of the cartilage defect were grouped into traumatic (7.0%), degenerative (52.0%), PTD (28.3%), and previous OD or flake fracture (12.6%). There were 61.5% of patients with OD or flake fracture who received additional surgery either before or parallel to ACI treatment such as implantation of an autologous spongiose graft (n = 11), Pridie drilling (n = 10), or osteochondral refixation (n = 5) (Table 2). There were 29.8% of patients with no previous surgery of the knee who were eventually treated; in 16.2% of patients, multiple

<table>
<thead>
<tr>
<th>Additional Surgery</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous spongiosa graft</td>
<td>11</td>
</tr>
<tr>
<td>Pridie drilling</td>
<td>10</td>
</tr>
<tr>
<td>Flake fracture refixation</td>
<td>5</td>
</tr>
<tr>
<td>Mosaicplasty</td>
<td>3</td>
</tr>
<tr>
<td>Microfracture</td>
<td>2</td>
</tr>
<tr>
<td>Sandwich technique</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>19</td>
</tr>
</tbody>
</table>

*Patients frequently received additional surgery either before autologous chondrocyte implantation (ACI) or as parallel treatment in the same session with ACI.*
### Previous Surgery

The American Journal of Sports Medicine

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Percentage of the Variable</th>
<th>No Revision, n</th>
<th>Revision, n</th>
<th>Treatment Failure, %</th>
<th>Odds Ratio</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>413</td>
<td>100.0</td>
<td>325</td>
<td>88</td>
<td>21.3</td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;30</td>
<td>123</td>
<td>28.8</td>
<td>99</td>
<td>24</td>
<td>19.5</td>
<td></td>
<td>.595</td>
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<td>30-89</td>
<td>179</td>
<td>43.8</td>
<td>140</td>
<td>89</td>
<td>21.8</td>
<td>1.2</td>
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<tr>
<td>≥40</td>
<td>111</td>
<td>28.9</td>
<td>86</td>
<td>25</td>
<td>22.5</td>
<td>1.2</td>
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<tr>
<td>BMI, kg/m²</td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>232</td>
<td>56.2</td>
<td>177</td>
<td>55</td>
<td>28.7</td>
<td></td>
<td>.287</td>
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<tr>
<td>25-29</td>
<td>149</td>
<td>36.1</td>
<td>124</td>
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<td>16.8</td>
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<td>≥30</td>
<td>32</td>
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<td>No. of defects</td>
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<tr>
<td>1</td>
<td>340</td>
<td>82.3</td>
<td>286</td>
<td>74</td>
<td>21.8</td>
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<td>&gt;1</td>
<td>73</td>
<td>17.7</td>
<td>59</td>
<td>14</td>
<td>19.2</td>
<td>0.9</td>
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<td>Defect size, cm²</td>
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<td>&lt;3</td>
<td>44</td>
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<td>≥3</td>
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<td>59.4</td>
<td>233</td>
<td>76</td>
<td>20.8</td>
<td>0.9</td>
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*Supplemented by odds ratio for each parameter compared to the first of the category. BMI, body mass index; PTD, prolonged traumatic-degenerative; OD, osteochondritis dissecans; MFC, medial femoral condyle; LFC, lateral femoral condyle; BMS, bone marrow stimulation.

*Related P value (likelihood ratio test).

*P value of Pearson χ² test.

*P < .05.

previous surgeries (arthroscopy, meniscal surgery, reconstruction of a cruciate ligament, a lateral release, or other previous surgery) (Appendix, available online) had been performed. Within the group of patients in whom previous surgical interventions had been indicated, 30.0% of all patients had previous cartilage treatment (pretreatment)
vol. 40, no. 1, 2012

Need for Reintervention After ACI

Figure 1. Overall survival function with end-point revision surgery versus end of observation period for all patients (A) and "failure function" with end-point revision surgery for only the revision cohort (B). Most revision surgeries were performed during the first 3.5 years after autologous chondrocyte implantation (ACI).

(Appendix, available online), mainly microfracture (77 patients) or Pridie drilling (30 patients); 17 patients (4.2% of the basic population) had previous ACI at the same location of the knee joint. Parallel treatment was applied in 26.9% of the operative procedures, consisting of anterior cruciate ligament reconstruction, high tibial osteotomy, or rebalancing patella surgery (Appendix, available online). A total of 9.0% of the patients received other cartilage treatment (Appendix, available online). A total of 9.0% of the patients received other cartilage treatment during the same operative procedure in another joint (Appendix, available online). The odds ratio, the factor by which the risk for reintervention is increased compared with the control group, was calculated in the \( \chi^2 \) test. Both of these statistics consider each parameter individually, without implicating confounding bias. Taking into account confounding bias due to other observed parameters, statistical analysis with multivariate binary logistic regression was performed, which revealed identical qualitative results, with selection of the 4 parameters mentioned above showing a significant influence (Table 4). Subsequently, (1) female gender \( (P = .015; \text{odds ratio}, 1.7) \), (2) more than one previous surgery \( (P < .001; \text{odds ratio}, 4.0) \), (3) previous BMS \( (P = .017; \text{odds ratio}, 1.9) \), and (4) periosteum patch-covered technique \( (P = .031; \text{odds ratio}, 2.4) \) increased the risk for the need of reintervention.

Thus, no significant influence of age, BMI, amount of transplants, size, origin, location, nicotine consumption, and parallel treatment could be revealed. However, tendencies could be observed \( (P \) values given from Pearson \( \chi^2 \) test if not stated otherwise) (Table 3).

Despite a slightly increasing revision rate with age, there was no significant difference \( (P = .886) \). Intermediate BMI \( (25-29 \text{ kg/m}^2) \) showed the lowest revision rate. However, neither total \( P \) value \( (P = .237) \) nor \( P \) value comparing BMI of 25 to 29 \text{ kg/m}^2 with BMI \( \geq 30 \text{ kg/m}^2 \) \( (\chi^2 \text{ test}; P = .290) \) was significant. Multiple transplants (either in the same or different knee compartment) did not show a higher risk \( (\text{odds ratio}, 0.9; P = .624) \). The ACI at locations with previous OD or flake fracture \( (\text{odds ratio}, 1.1) \), acute traumatic \( (\text{odds ratio}, 1.5) \), and PTD lesions \( (\text{odds ratio}, 1.1) \) showed a comparable rate of later revision surgery with degenerative lesions \( (P = .811) \). Defects localized at the trochlea seemed to be associated with slightly better outcomes but not significantly \( (\text{odds ratio}, 0.7) \). The ACI at the patella had a comparable outcome to the ACI at the MFC or LPC. Multiple locations did not have an outcome significantly worse than other groups \( (\text{odds ratios}, 0.7-1.4; P = .796) \). The \( \chi^2 \) test revealed an odds ratio of 1.4 for patients with nicotine consumption compared to nonsmokers, which also was not significantly different.
(P = .228). Despite a lower revision rate for a larger defect size (odds ratio, 0.9), no significance was found for this parameter (P = .307). Parallel treatment also did not have an influence on the risk for resurgery after ACI (odds ratio, 0.3; P = .622).

Comparable results were found for prognostic factors using a Cox regression model for survival analysis (parametric survival fit), confirming our findings by eliminating differences in time of follow-up (Table 4). Time to event was defined as time to revision surgery versus end of follow-up because of this study. Significance was again observed for gender (P = .038), presurgery (P = .002), pre-treatment (P = .041), and surgical technique (P = .028). In the forward and backward Cox regression model, these 4 identified risk factors were also isolated and therefore display the qualitatively identical results compared to the binary logistic regression model.

**DISCUSSION**

The aim of the present study was to identify risk factors associated with the need for revision surgery after ACI. While previous studies evaluated reasons for failure by evaluating intraoperative findings during revision surgery to describe characteristic complications, this study was set up to identify risk factors within the entire population of ACI patients that increase the probability of reintervention. Even if the indication for reintervention is often based on individual patient characteristics and tends to depend on the treating surgeon, all patients who underwent reintervention after ACI are comparable. This comparability is related to the fact that persistent functional limitations were present in all cases. Therefore, need for reintervention was considered an appropriate parameter indicating a nonsatisfying clinical course after ACI.

The time from ACI to reintervention was on average 1.8 years. Overall, the reintervention rate in the present study was 21.8%. Comparing the revision rate in 1997 to 1998 with the revision rate 10 years later (2007-2008), it decreased by more than two-thirds (36.8% vs 10.3%), explaining the overall revision rate. This rate compares well with previous studies. The overall revision rate of all techniques was reported to be 38%, while periosteum patch-covered technique presents a higher failure rate than other techniques.

In this context, it needs to be clarified that although all patients who underwent reintervention reported persistent pain or limited knee function, the indication for reintervention does not necessarily have to be a treatment failure. Complications in the clinical course after ACI that can sufficiently be handled arthroscopically and at low risk for the individual patient while preserving the transplant can be found. Some of these techniques have been shown to improve the function of the affected knee and to help reduce pain, for example, debridement of a hypertrophic transplant or microfracture of an adjacent defect. Hypertrophic transplants were not defined as "treatment failure" by Minas et al because they were not treated by removal of more than 25% of the graft area or by violating the subchondral bone. In addition, in the postoperative course after ACI, MRI findings do not seem to be sufficiently correlated with postoperative knee function in every single patient, and some of the typical complications are characterized by unspecific MRI findings. This also justifies the indication for re-arthroscopy of the affected joint, so that an overall rate of approximately 20% seems acceptable.

Obviously, the study design using "need for revision" as a single parameter to address the success of the ACI procedure differs from the analysis of knee function using standard scoring systems for postoperative evaluation in that minor differences between these subgroups might not be detected and the revision rate remains equal even if a large number of patients is evaluated. Therefore, it cannot be concluded that functional outcome is identical in these sub-populations. Simply, the overall failure rate seems similar.

Concerning risk factors associated with the need for reintervention, odds ratio was calculated, and the Pearson \( \chi^2 \) test for every single parameter was used. Yet, our data were clearly strengthened through the use of multivariate binary logistic regression and Cox regression model for

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*Results of statistical analysis with multivariate binary logistic regression, forward logistic regression, and Cox regression model for survival analysis (parametric survival fit). Female gender, more than one previous surgery, previous bone marrow stimulation (BMS), and periosteum patch-covered autologous chondrocyte implantation (ACI) technique were identified by both statistics to be associated with an inferior outcome. \( P < .05 \).
survival analysis, both including forward regression and backward regression. All parameters evaluated in the present study were considered. In both of the tests, qualitatively identical results were observed, demonstrating strong data robustness. This underlines importance, validity, and explanatory power of this study. Regression statistics constantly eliminated existing confounding bias in the large patient cohort and reduced the influence factors to those that presented an influence on the outcome in any variable subgroup.

Regarding the results, in every statistic used, the same 4 factors could clearly be identified to influence the outcome of ACI negatively: female gender, more than one previous surgery, previous BMS, and periosteum patch-covered technique. All of the other parameters did not show a significant difference, although tendencies could be seen considering odds ratio. The factors evaluated presented different quality characteristics. They included patient-specific parameters (such as gender, age, etc), defect-specific parameters (such as defect size and defect location), technical aspects (such as the type of ACI used), and parameters dealing with the individual history of the patient (such as number and type of prior surgeries).

Concerning patient-specific risk factors for "need of reintervention," we found a significantly higher incidence of reinterventions in the subgroup of female patients (26.7%) compared with male patients (17.3%; odds ratio, 1.7; P = .021). This parameter was also significantly stronger in the Cox regression model (P = .083). Interestingly, some previous studies were not able to demonstrate an influence of gender on clinical outcome, but also found a better clinical outcome for men.

Other patient-specific parameters such as age and BMI failed to show statistical significance. The revision rate was only slightly increased between the age groups. As one of the contrasting findings, BMI was not significantly associated with an increased risk for reintervention (P = .287). This observation is in contrast to overweight-related increased risk for osteoarthritis of the knee joint. An increased BMI is associated with an unfavorable clinical course of osteoarthritis. This information cannot be drawn from our cohort of patients where existing osteoarthritis is defined as an exclusion criterion for ACI. Therefore, the missing influence of body weight on the outcome can partially be explained by selection of the patients for whom the indication for ACI was made. Patients with high BMI, noncompliancy, and extensive osteoarthritis had contraindications for treatment with ACI. However, reintervention rate was the lowest for the intermediate (overweight) BMI group (16.8%) compared with male patients (17.3%; odds ratio, 1.7; P = .021). This parameter was also significantly stronger in the Cox regression model (P = .083). Interestingly, some previous studies were not able to demonstrate an influence of gender on clinical outcome, but also found a better clinical outcome for men.

As the last patient-specific parameter, nicotine abuse could not be identified as a highly ranked risk factor for need for revision surgery. In previous studies, inferior results for ACI in smokers or ex-smokers were observed. To some extent, higher relative risk was observed in our present study for smokers as well, although not significantly different (odds ratio, 1.4; P = .288). Nicotine shows a toxic effect on chondrocytes, delays chondrogenesis, induces degeneration, and is correlated with a higher incidence of cartilage defects. Consequently, it seems logical that nicotine influences cartilage replacement therapies. On the other hand, a positive influence on collagen synthesis of chondrocytes was observed. As it is not known at which time point nicotine abuse has the most negative effect on transplanted chondrocytes, to some extent, the missing time resolution of smoking can explain the missing significance. It seems obvious that especially during the first weeks after transplantation, the cells are most sensitive for toxic effects during proliferation and extracellular matrix production. Although missing significance using statistically hard criteria, it is probably advisable to recommend a reduction of nicotine abuse.

Other parameters deal with the individual history of the patient. In this context, as one of the most relevant parameters correlating with the need for reintervention identified in this study, prior surgical treatment needs to be addressed. While only one prior surgery did not significantly increase the risk for need of reintervention (odds ratio, 1.4), patients with 2 or more prior surgeries had a 4.0-fold increased risk. When taking a closer look at the prior treatment of the cartilage defect, the risk of reintervention was significantly highest in the subgroup of patients previously treated with BMS techniques such as antegrade drilling or arthroscopic microfracture (odds ratio, 1.9; Cox survival analysis: P = .041), while those patients with a previous transplantation technique such as ACI only showed an increased risk of 1.2 for the need of revision surgery. While previous surgeries were identified as a negative prognostic factor in ACI, these data suggest that specifically BMS techniques seem to be associated with a higher risk of failure after ACI. This has already been demonstrated by Minas and coworkers, who found a 3-fold increased risk for failure of ACI if previous BMS was performed. Additionally, our data contribute to this observation that obviously a previous transplantation is not associated with such a high risk of unfavorable outcome. A possible explanation could be that BMS also affects the subchondral bone, which in general is not the case for ACI. In case of ACI after BMS technique, the ACI is applied on a modified subchondral bone, and an initial chondral problem could have been transferred into an osteochondral abnormality. This interpretation might explain why, after previous transplantation techniques such as the ACI, the risk for reinterventions does not seem to be significantly raised in contrast to prior BMS. Thus, ACI should be regarded as a first-line instead of a second-line treatment in patients with isolated cartilage defects of the knee joint. The origin of the defect itself did not have a relevant influence on the outcome, although the odds ratio was raised for traumatic mechanism of injury. Consequently, configuration of the defect seems to be more important than the origin of the defect itself.

The risk for reintervention did not appear to be significantly associated with the defect-specific parameter "defect size," which seems important because an inferior outcome
for larger defects has been reported for microfracture. Most surgeons indicate ACI for lesions larger than 3 cm². Our study revealed an even lower revision rate for larger lesions (odds ratio, 0.9) and only 7% revision surgery for very large lesions of more than 10 cm². Also, Maus et al especially achieved good results for large lesions. This might be justified by a particularly good improvement compared with the preoperative status. Consequently, it seems more important to allow a sufficient attachment to adjacent cartilage because malfusion is a common cause for revision surgery (Table 1), rather than restricting ACI size. Further defect-specific parameters such as number of defects treated (P = .624) and defect location (P = .796) failed statistical significance. These observations are in contrast to prior studies that described inferior results in patients with multiple defects, as well as in patients with defects located on the patella. This observation might be because of strict abidance of recommended indications versus contraindications preoperatively. Interestingly, this observation is in line with the finding that retropatellar "double-eye" technique is more physiological and shows good results.

Three different technical modifications of ACI have been used in the present patient population, including the first- and second-generation ACI as well as a third-generation product. As already demonstrated in earlier studies, revision and failure rates were significantly highest in the first-generation ACI group (31.2%; Cox survival analysis: P = .028), while no difference between the second- and third-generation product could be identified (reintervention rate, 18.3% and 15.9%, respectively). The increase of the rate of hypertrophic transplants might cause the increase of the rate of reinterventions in the periosteum group, but this high incidence of reinterventions must be considered against the background that this complication can be handled easily and cannot be put on a level with treatment failure.

In a quarter of the patients included in the present study, ACI was performed together with concomitant surgeries (Appendix, available online). This was because of the background that cartilage defects should also be regarded and treated in the context of other abnormalities (such as ligament instabilities or skeletal malalignment). The fact that the rate of reinterventions was comparable in the group of patients in which concomitant surgery had been performed (19.6% vs 21.9%; P = .622) underlines the importance of the treatment of concomitant abnormalities if they are indicated.

There are several limitations of our study. First, different surgeons performed the ACIs during the assessed 12 years. Yet, regarding the large cohort of more than 400 patients and the long observation interval, this small number of surgeons seems quite good. Second, because of slightly higher mean follow-up times for first-generation ACI technique, the difference to other techniques might be a little overestimated. However, the mean failure at 1.8 years lay within the complete observation period, and by applying Cox survival analysis, the observation period does not influence the revealed significance of this risk factor, only the dimension. It is likely the follow-up time for all techniques will need to be extended in future studies.

In conclusion, the present study identifies various risk factors that are associated with the need for revision surgery after ACI in a large study population of a total of 413 patients. Four statistically relevant factors, namely, female gender, previous surgery at the treated joint, previous BMS, and periosteum patch-covered ACI technique, were identified. Other parameters showed tendencies regarding their relative risk without being significant in the strict regression model. Most factors identified here with prediction for negative outcome or factors showing a tendency can be detected and influenced either by the patient or by the surgeon (such as number and kind of prior treatment). In a clinical setup, all parameters should be taken into account and considered carefully prior to the ACI procedure in order to allow determination of an individual prognosis for each patient receiving ACI.

REFERENCES