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Repair of Focal Cartilage Defects With Scaffold-Assisted Autologous Chondrocyte Grafts

Clinical and Biomechanical Results 48 Months After Transplantation

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Background: Scaffold-assisted autologous chondrocyte implantation is a clinically effective procedure for cartilage repair, but biomechanical evaluations are still missing.

Purpose: This study was conducted to assess the clinical efficacy, including biomechanical analyses, of BioSeed-C treatment for traumatic and degenerative cartilage defects of the knee.

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

Methods: The authors evaluated the midterm clinical and biomechanical outcome of BioSeed-C, a cell-based fibrin-polymer graft for the treatment of cartilage defects. Clinical outcome at 4-year follow-up was assessed in 52 patients with full-thickness cartilage defects, International Cartilage Repair Society (ICRS) stage III and IV. Clinical scoring was performed preoperatively and 48 months after implantation using the Lysholm score, the International Knee Documentation Committee (IKDC) score, the ICRS score, the Knee injury and Osteoarthritis Outcome Score (KOOS), and the Noyes score. Cartilage regeneration was assessed by magnetic resonance imaging (MRI) using the Henderson-Kreuz score. Biomechanical evaluation was performed by isokinetic strength measurements, comparing healthy and operated knee of each patient.

Results: Clinical evaluation showed significant improvement in the Lysholm (from 51.8 preoperatively to 80.7 at 48 months postoperatively), IKDC (from 47.5 to 71.5), ICRS (from 3.8 to 2.0), KOOS (subcategory pain from 62 to 78, symptoms from 68 to 76, activities of daily living from 68 to 85, sports from 19 to 55, and quality of life from 30 to 55), and Noyes (from 31 to 59) scores ($P \leq .001$) 48 months after implantation of BioSeed-C compared with the preoperative situation. The MRI evaluations showed moderate to complete defect filling in 43 of 44 treated patients. Two patients without improvement in the clinical and MRI scores received a total knee endoprosthesis after 4 years. Isokinetic evaluation showed significantly reduced maximum strength capacities for knee flexion and extension at the operated knee compared with the healthy knee ($P < .05$).

Conclusion: The clinical outcomes 4 years after graft implantation are good despite a persisting strength deficit. Implanting BioSeed-C is a promising treatment option for cartilage defects of the knee. More emphasis should be put on the rehabilitation of muscular strength.

Keywords: scaffold-assisted autologous chondrocyte implantation; BioSeed-C; clinical efficacy; focal cartilage defects; midterm results; isokinetic strength measurement

Cartilage has a low self-healing capacity. In clinical routine, a variety of surgical techniques for articular cartilage repair have been established,[14,45] including bone-marrow–stimulating techniques, osteochondral autograft transfer, and common autologous chondrocyte implantation (ACI).[12,29,46] Treatment options have to be chosen individually, depending on the defect size, depth, and location. Especially for large cartilage defects, cell-based cartilage repair approaches based on matrices support the formation of hyaline-like repair tissue[20] and provide long-term clinical effects and patient improvement.[13,19,40]

As reported by Minas in 2003,[32] more than 15 000 patients worldwide have been treated with ACI since Brittberg et al[12] introduced this technique in 1987. Since the establishment of the procedure, a variety of clinical studies

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have confirmed the clinical efficacy of implanting autologous in vitro–expanded chondrocytes for the regeneration of cartilage defects.[13,19,39] In the first-generation and second-generation ACI, the prepared defect is covered with a periosteal flap or a collagen sheet that is fixed to the intact cartilage rim before the autologous chondrocyte cell suspension is injected. The use of ACI may therefore be difficult in some regions of the knee, especially in defect locations lacking a stable cartilage shoulder. Disadvantages of this first-generation treatment option were periosteal hypertrophy, ablation, and loss of cells into the joint cavity,[15,30,35] leading to a revision surgery rate of up to 25% to 40%.[18,31,48]

Therefore, in scaffold-assisted ACI, cartilage tissue–engineering grafts combining ACI with stable 3-dimensional matrices were developed to overcome these disadvantages. These grafts ensure the 3-dimensional distribution of the in vitro–cultured chondrocytes, provide an initial mechanical stability for an easy handling by the surgeon,[43] and promote chondrocyte differentiation and subsequent formation of hyaline-like cartilage repair tissue. Based on this concept, scaffold-assisted chondrocyte implantation with scaffolds of hyaluronan,[28,34,47] collagen,[8-10] and resorbable polymers[23,36] were shown to be clinically efficient for the repair of cartilage defects.

In BioSeed-C (BioTissue Technologies GmbH, Freiburg, Germany), the chondrocytes are embedded in a stable fibrin-polymer matrix, which allows an arthroscopic implantation and ensures a secure fixation of the graft.[16] In a horse model, formation of a hyaline-like cartilage matrix as well as firm bonding of the graft to the adjacent healthy cartilage and subchondral bone could be shown.[4] Recently, midterm clinical results with 2-year follow-up[36] and clinical outcome after 4 years in an osteoarthritis subgroup[23] confirmed the clinical efficacy of this scaffold-assisted ACI. Until now biomechanical studies with muscle strength measurement are missing for all ACI techniques.

The aim of this prospective study was to evaluate the midterm clinical outcome of BioSeed-C for the treatment of focal cartilage defects of the knee including clinical, functional, and biomechanical analyses.

MATERIALS AND METHODS

Patients

In this prospective study, the effectiveness of scaffold-assisted ACI (BioSeed-C) for the treatment of chondral defects of the knee 4 years after transplantation was investigated.

From December 2001 to October 2002, 79 patients suffering from shouldered, focal posttraumatic or degenerative symptomatic cartilage defects of the knee with Outerbridge classification IV were treated with BioSeed-C. Two-year follow-up data of this particular patient population (n = 40 patients) as well as analysis of the osteoarthritis subgroup at 4 years (n = 19 patients) were published previously.[23,36] In this study, 52 patients gave consent to a clinical follow-up of 4 years. For 19 of 52 patients, radiographs were available showing a Kellgren-Lawrence score of 2 or 3. These defects were classified as focal degenerative, osteoarthritic defects.[23] Clinical and functional evaluations were performed comparing the patients' situations preoperatively and at 48 months after transplantation by clinical and functional scores, MRI score, and comparative isokinetic examinations of the knees. The patient characteristics are presented in Table 1.

The average age of the patients (25 females and 27 males; mean body mass index [in kg/m^2] of 24.95, ranging from 19-34) was 35.59 years (range, 17-51 years). The mean defect size of the first lesion was 4.76 cm^2 (range, 2-15 cm^2) with Outerbridge classification IV.[37] Chondral defects were located on the femoral condyles (n = 31), retropatellar (n = 13), tibia (n = 1), and on the trochlea (n = 7). Two secondary lesions were treated with BioSeed-C as well. Previous surgical procedures were anterior cruciate ligament/collateral ligament reconstruction (n = 13), lateral release (n = 1), drilling or microfracture (n = 10), shaving (n = 23), abrasion arthroplasty (n = 6), ACI (n = 2), meniscectomy (n = 29), and high tibial osteotomy (n = 6). When implanting BioSeed-C, 25 concomitant surgical procedures were performed, such as anterior cruciate ligament reconstruction (n = 6), patella balancing (n = 2), drilling/microfracture (n = 5, secondary lesions), high tibial osteotomy (n = 10) and subchondral bone grafting (n = 2). Indications for high tibial osteotomy were varus or valgus malalignment exceeding 5° and patella balancing was performed in patients with a patella malalignment with a medial or lateral shift >0.5 cm. Axial deformities were analyzed by radiographs of the whole leg and the correct patella position was detected by a routine mediolateral, femoropatellar, and axial joint radiograph.

Implantation of BioSeed-C

From a lower weightbearing area of the knee, approximately 250 mg of the patient's healthy cartilage was harvested arthroscopically and autologous chondrocytes were

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TABLE 1
Patient Characteristics

Characteristic	Patient Data
Sex	Female, n = 25 Male, n = 27
Age, y	35.59 (range, 17-51)
Body mass index, kg/m^2	24.95 (range, 19-34)
First lesion	
Defect size, cm^2	4.76 (range, 2-15)
Outerbridge classification	IV (n = 52)
Localization, no.	
Femoral condyle	31
Retropatellar	13
Trochlea	7
Tibia	1
Second lesion	
Defect size, cm^2	2.63 (range, 0.5-4)
Outerbridge classification	III-IV
Localization, no.	
Medial femoral condyle	1
Lateral femoral condyle	3
Trochlea	6
Retropatellar	2
Concomitant surgery, no.	
Anterior cruciate ligament reconstruction	6
Patella balancing	2
Microfracture/drilling	5
High tibial osteotomy	10
Subchondral bone grafting	2
Previous surgical procedures, no.	
Anterior cruciate ligament/ collateral ligament reconstruction	13
Lateral release	1
Microfracture/drilling	10
Shaving	23
Abrasion arthroplasty	6
Autologous chondrocyte implantation	2
Meniscectomy	29
High tibial osteotomy	6

isolated. For autologous chondrocyte cultivation, 100 mL of whole blood was collected with a conventional blood sampling system (Sarstedt AG, Nümbrecht, Germany). After in vitro expansion, approximately 20 million chondrocytes were rearranged in a 3-dimensional polymer-based scaffold, made of polyglycolic/polylactic acid (polyglactin, Vicryl [Ethicon GmbH, Norderstedt, Germany]) and polydioxanone by fibrin gluing. After debridement of the cartilage defect zone down to the subchondral bone, the in vitro cultured graft (2 cm × 3 cm × 0.2 cm thick) was cut to the size of the defect and implanted through arthrotomy or arthroscopy into the defect area. The use of the arthroscopic approach or mini-open arthrotomy depended on the location and size of the defects. In total, 72 of 79 patients received BioSeed-C by arthrotomy, while arthroscopy was used in 7 patients. Arthroscopic implantation was performed when defects were located on the medial/lateral condyle and when only 1 graft was sufficient to cover the defect. For stable fixation, the graft was fixed with resorbable suture material by a previously described anchor-knot technique.[16,23,36]

Follow-up Treatment After Transplantation of BioSeed-C

The day after surgery, rehabilitation started, including mobilization on crutches with a maximal loading 15% body weight, continuous passive motion, and range of motion (ROM) exercises. The ROM was limited to 30° after retropatellar transplantation. Passive ROM exercises were gradually increased to self-assisted exercises. Continuous passive motion for 6 hours per day and partial loading with 15% body weight was maintained for 6 weeks.[24,46] After this period, patients gradually increased the loading and performed increased strength training as well as active physiotherapy and gentle ergometric training at an appropriate level for the next 6 weeks. Starting as week 13, patients increased weightbearing and performed strength training and coordination exercises up to full weightbearing. After 6 months, cycling or jogging was allowed, followed by more strenuous activities and contact sports after the first rehabilitation year. Patient compliance for rehabilitation was not monitored.

Evaluation of Clinical, Functional, and Biomechanical Results

Clinical outcome could be evaluated in only 50 of 52 patients, because in 2 patients total knee replacement was necessary during the follow-up period. Clinical results were evaluated by the International Knee Documentation Committee (IKDC) score,[21] the International Cartilage Repair Society (ICRS) Knee Examination Form,[1] the Lysholm score,[27] the Noyes activity rating score,[3] and the Knee injury and Osteoarthritis Outcome Score (KOOS).[42] For each score, the data were documented preoperatively and at 48 months after surgery.

After 4 years of follow-up, 43 patients gave consent to participate in isokinetic testing and 44 patients allowed secondary MRI. At 4 years after transplantation, MRI of the knee was accomplished with a 1.5-T scanner (Siemens AG, München, Germany) and the data were evaluated using the modified Henderson and Kreuz scoring system.[19,24] For biomechanical evaluation, maximum strength was measured in 2 different concentric and 1 eccentric test modes at 60 and 180 deg/s using an isokinetic dynamometer (CON-TREX MJ Multi-joint Module, CMV AG, Dübendorf, Switzerland). Five reciprocal flexion and extension movements were performed with the healthy and the operated knee in the different test modes (concentric 60 deg/s, concentric 180 deg/s, and eccentric 60 deg/s). Thereby, reciprocal knee flexion and extension movements were performed to measure quadriceps and hamstring strength capacities in Newton-meters.

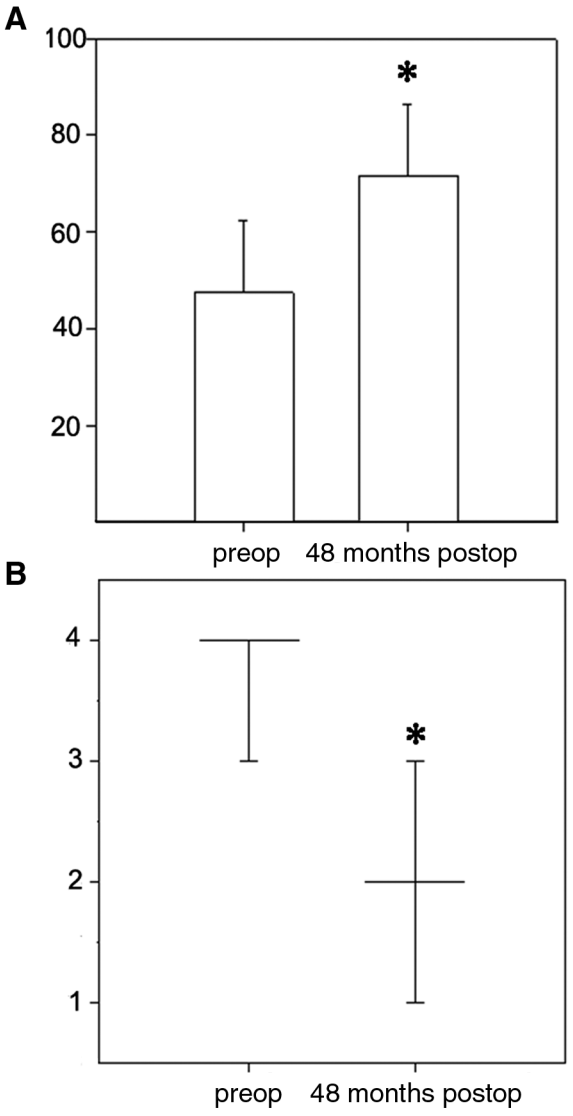

Figure 1. Clinical outcome after 4 years as evaluated by using the International Knee Documentation Committee (IKDC) score and the International Cartilage Repair Society (ICRS) score. Asterisks indicate a statistically significant difference ($P \leq .001$) at 48 months after transplantation compared with the preoperative situation. A, statistical analysis of the clinical outcome as assessed by the IKDC subjective knee evaluation score was performed using a parametric Student *t* test ($P \leq .001$). Scores are presented as the mean with error bars defining the standard deviation. B, the ICRS scores were analyzed statistically using the nonparametric Mann-Whitney rank-sum test. Scores are presented as the median, with bars defining the 25th and 75th percentiles and error bars defining the 10th and 90th percentiles.

Statistical Analysis

For statistical analysis, data were proofed by normality test ($P > .050$) for parametric or nonparametric distribution. Subsequently, for nonparametric data, the Mann-Whitney rank-sum test was applied and differences were considered significant at $P < .05$. The IKDC data and the KOOS subcategory symptoms data were analyzed by parametric Student *t* test. Differences were considered significant at $P < .05$. All comparisons were performed between scorings preoperatively and scores at 48 months after surgery. The Wilcoxon test was used to analyze nonparametric biomechanical data at 4-year follow-up, performed on the healthy and operated knee of each patient. Differences were considered significant at $P < .05$.

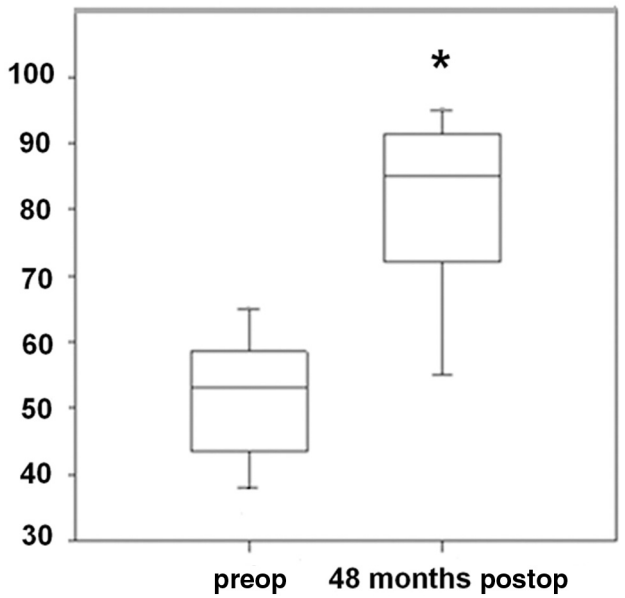

Figure 2. Clinical outcome after 4 years as evaluated by the Lysholm score. Statistical analysis of the clinical outcome was performed using the Mann-Whitney rank-sum test. Scores are presented as the median with the end of the boxes defining the 25th and 75th percentiles and error bars defining the 10th and 90th percentiles. The asterisk indicates a statistically significant difference ($P \leq .001$) compared with the preoperative situation.

RESULTS

Clinical Evaluation
4 Years After Implantation of BioSeed-C

The clinical outcome 4 years after implantation of BioSeed-C in focal cartilage defects was evaluated using the IKDC knee evaluation score and the ICRS score (Figure 1). The IKDC score (Figure 1A) showed significant improvement at 4 years ($P \leq .001$) postoperatively compared with preoperative findings in 50 patients, showing an increased mean score from 47.5 to 71.5. The IKDC scores were rated abnormal in 98% of the patients at baseline and improved to a normal or nearly normal rating in over 80% of the patients at follow-up. In addition, the

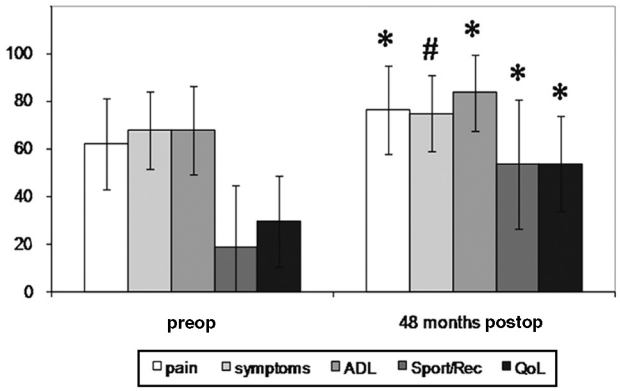

Figure 3. Clinical outcome after 4 years as evaluated by the Knee injury and Osteoarthritis Outcome Score (KOOS) in 46 patients. The KOOS is presented as a mean value with error bars defining the standard deviation. Asterisks indicate a statistically significant difference ($P \leq .001$) at 48 months after transplantation compared with the preoperative situation as assessed by nonparametric Mann-Whitney rank-sum test. The hatch mark indicates a statistically significant difference ($P < .05$) at 48 months after transplantation compared with the preoperative situation as assessed by parametric Student *t* test. ADL, activity of daily living; Sports/rec, sports and recreation; QoL, quality of life.

ICRS score improved significantly ($P \leq .001$) over the observational period from 3.8 preoperatively to 2.0 at 4-year follow-up (Figure 1B).

Four years after graft transplantation, clinical evaluation as assessed by the Lysholm score showed statistically significant improvement ($P \leq .001$). Compared with the patients' preoperative situation, the median Lysholm score improved significantly ($P \leq .001$) from 51.8 to 80.7 in the study population (Figure 2).

Further clinical and functional evaluation was assessed by the KOOS and the Noyes score. After 48 months, the patients' status improved significantly ($P \leq .001$) compared with preoperative findings in the subcategories pain, activities of daily life (ADL), sports and recreation (Sports/rec), and quality of life (QoL) (Figure 3). The mean scores increased in the subcategories pain from 62 to 78; ADL, from 68 to 85; Sports/rec, from 19 to 55; and knee-related QoL, from 30 to 55 at 4 years after implantation of the graft. Patients also showed a significant improvement in the subcategory symptoms (from 68 to 76) as analyzed by paired *t* test ($P < .05$) at 4-year follow-up. Individual preoperative and 4-year follow-up scores (ICRS, IKDC, KOOS, and Lysholm) are given in the supplementary material (see Appendix 1, available in the online version of this article at http://ajs.sagepub.com/supplemental/).

For further functional analysis, the Noyes activity rating score was used (Figure 4). At 48 months after implantation, the Noyes score improved significantly ($P \leq .001$) with increased median scores going from 31 preoperatively to 59 after the observational period of 4 years.

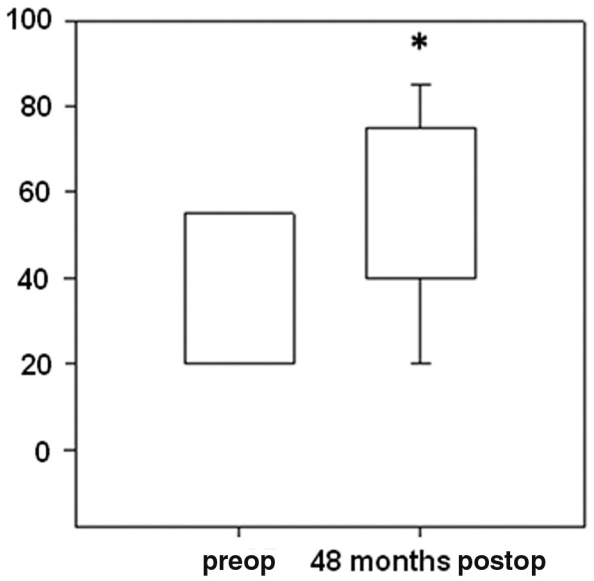

Figure 4. Clinical outcome after 4 years as evaluated by the Noyes activity rating score. The Noyes scores were statistically analyzed by the Mann-Whitney rank-sum test. Scores are presented as the median with the end of the boxes defining the 25th and 75th percentiles and error bars defining the 10th and 90th percentiles. The asterisk indicates a statistically significant difference ($P \leq .001$) at 48 months after transplantation compared with the preoperative situation.

Magnetic Resonance Imaging and Evaluation 4 Years After Graft Transplantation

A detailed MRI analysis according to Henderson and Kreuz is given in Table 2. Therein, 44 of 52 patients were analyzed by MRI 4 years after implantation of BioSeed-C. Two patients had to undergo revision surgery and received a total knee endoprosthesis and a further 6 patients without pain or clinical problems refused to provide radiologic data for our 4-year follow-up. These patients are not included in the table data. Patients with focal cartilage defects treated with BioSeed-C showed moderate to complete filling of the defects. Thirty-two of 44 patients showed a complete filling of the defect with cartilage repair tissue. In 11 patients, the defects were filled incompletely but more than 50% and 1 patient showed a defect filling of less than 50%. The cartilage signal in 26 defects was normal or showed slight alterations in the intensity in 15 patients. In 3 defects, the signal was hyperintense in larger areas of the repair tissue. Strong to moderate subchondral edema was evident in 8 patients and 36 of 44 patients showed no or mild edema. Seven patients showed moderate to strong signs of knee joint effusion. No or mild knee joint effusion was evident in 37 of 44 patients treated with BioSeed-C at 4-year follow-up. Both patients who received a total knee replacement after 4 years had the last MRI control 12 months postoperatively. In these 2 patients, the defects were partially filled (<50%)

TABLE 2
Magnetic Resonance Imaging Analysis of 44 Patients at 48 Months After Graft Transplantation

Rating	Defect Filling	Signal Intensity	Subchondral Edema	Effusion
1 Normal	32 (complete filling), including 4 with minimal hypertrophy and 2 with subchondral cysts	26 (normal)	14 (no edema)	10 (no effusion)
2 Mild	11 (>50%), including 3 with minimal hypertrophy and 2 with subchondral cysts	15 (small hyperintense areas)	22 (mild edema)	27 (mild effusion)
3 Moderate	1 (<50%)	3 (hyperintense areas)	7 (moderate edema)	6 (moderate effusion)
4 Abnormal	0 (no filling)	0 (no signal)	1 (distinct edema)	1 (distinct effusion)

with a hyperintensive repair tissue and showed a concomitant moderate subchondral edema.

Biomechanical Evaluation
4 Years After Implantation of BioSeed-C

In 43 of 52 patients, maximum strength of the knee flexors and extensors at 4-year follow-up was assessed isokinetically (3 different test modes: concentric 60 deg/s, concentric 180 deg/s, and eccentric 60 deg/s) using the CON-TREX multijoint dynamometer (Figure 5). Two patients had to undergo revision surgery and received a total knee endoprosthesis, and in a further 7 patients no biomechanical data could be assessed because of limited patient compliance with participation. Data evaluation by Wilcoxon test comparing healthy and treated knees of each patient revealed significantly ($P < .05$) higher peak torques in the healthy knee in all test modes. The differences in maximum strength were not as high in knee flexion as in knee extension (Figure 5B), indicating an imbalance of the quadriceps and hamstring on the operated side (Figure 5A).

DISCUSSION

In the present study, we showed the benefit and reliability of the use of the autologous gel polymer–based tissue-engineering graft BioSeed-C for the treatment of full-thickness posttraumatic or degenerative cartilage defects in the knee. All of the 4 validated scores used in this study showed a statistically significant improvement ($P < .05$) 4 years after scaffold-assisted ACI. The mean IKDC score increased from 47.5 preoperatively to 71.5 at 48 months. The IKDC scores were rated abnormal in 98% of the patients at baseline and improved to a normal or nearly normal rating in over 80% of the patients at follow-up. These findings support the good results of Behrens et al,[10] Kon et al,[22] and Gobbi et al,[17] who found normal or nearly normal values in 70% of the patients at 36 months,[10] 81% at 60 months,[10] or 91% at 60 months[17] and mean IKDC values of 69 points,[10] 77 points,[17] and 80 points[22] 5 years after matrix-associated ACI. The scaffolds used in the mentioned studies are composed of different biomaterials such as collagen, polymers with fibrin glue, or hyaluronic acid. Nevertheless, all techniques belong to scaffold-assisted ACI and have been shown to be effective in the treatment of isolated cartilage defects in the knee.

Lysholm score values were 80.7 points at follow-up compared with preoperative values of 51.8 points. This shows that the loading capacity of the treated knee joint is well maintained at midterm. At 4-year follow-up, the KOOS improved in the subcategories pain, from 62 preoperatively to 78 postoperatively; symptoms, from 68 to 76; ADL, from 68 to 85; Sports/rec, 19 to 55; and QoL, 30 to 55. In the same study group at a 2-year follow-up, Ossendorf et al[36] reported a mean Lysholm score of 78 points at 2-year follow-up and improvement of KOOS values for pain from 64.3 preoperatively to 78.2 postoperatively; for symptoms, from 68.2 to 78.9; ADL, 67.6 to 80.6; Sports/rec, 25.8 to 45.7; and QoL, from 29.9 to 52.9. This shows that the patients' improvement remained stable and that the good results found in the short-term follow-up at 2 years could be confirmed in the midterm at 4-year follow-up.

Previously, we reported the 4-year clinical outcome of a subgroup of the study population with focal degenerative and/or osteoarthritic cartilage defects.[23] Interestingly, when comparing the traumatic and the osteoarthritic subgroups, we found no significant differences in the values for ICRS, IKDC, Lysholm score, and KOOS. This may indicate that the treatment with BioSeed-C leads to good clinical results in traumatic defects as well as in shouldered, focal degenerative defects.

The mean Lysholm score in our study was higher than the value of 63 reported by Pascual-Garrido et al,[38] also 4 years after ACI. The mean age of their patients was even lower in their collective but they included only patients treated for patellofemoral defects. This confirms the results of previous studies reporting worse results after ACI in patellofemoral compared with femoral condyle defects. Furthermore, the Lysholm score in our study was better compared with the average Lysholm score of 69.5 reported by Peterson et al[41] in their long-term follow-up of first-generation ACI. An explanation for these different results might be the use of another ACI technique or differences in the make-up of the patient cohort. The problems of first-generation ACI using a periosteal flap with hypertrophic changes, delamination, and osseous overgrowth are not described with the scaffold-assisted ACI technique.[23]

The KOOS results 4 years after using BioSeed-C showed that not only the knee function improved, but also subjective pain was reduced. The presented results for the

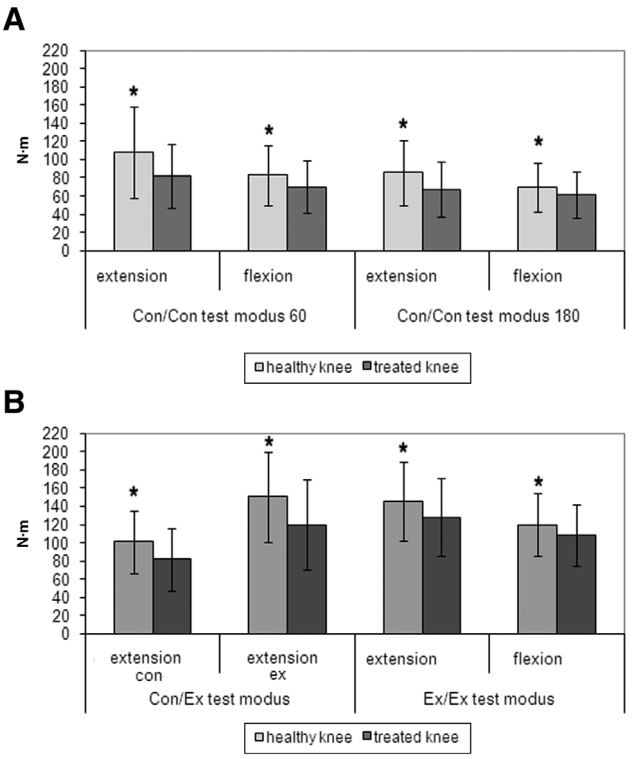

Figure 5. Biomechanical evaluation after 48-month follow-up performed on 43 patients. Reciprocal movements of the knee were performed for flexion and extension in 2 different angle speeds of 60 and 180 deg/s (A) and isokinetic single-joint maximum strength measurements were investigated in different concentric and eccentric test modes (B). Statistical evaluation was performed comparing healthy and treated knees by nonparametric Wilcoxon test. Statistically significant differences were considered at $P < .05$ and are indicated with asterisks.

KOOS are better than the results of the STAR (Study of the Treatment of Articular Repair) trial reported by Zaslav et al[48] and are again considerably higher than the 4-year results of Pascual-Garrido et al[38] in patellofemoral defects. They reported values of 71 points for KOOS pain compared with 77 points in our study, 70 (compared with 75) for KOOS symptoms, 80 (compared with 84) for KOOS ADL, 42 (compared with 54) for KOOS Sports/rec, and 49 (compared with 54) for KOOS QoL.[38] To summarize, the results of all clinical scores showed satisfying results of midterm outcome of BioSeed-C ACI, confirming the promising results of the previously reported 2-year results.

A limitation of the current study is the lack of repair tissue evaluation by, for example, second-look arthroscopy or analysis of cartilage repair tissue at midterm follow-up. However, 9 to 12 months after transplantation of BioSeed-C, second-look arthroscopy and histologic analysis of repair-tissue biopsy specimens showed that a tough, hyaline-like cartilaginous repair tissue developed in the same patient cohort.[36] Therefore, it is suggested that transplantation of BioSeed-C leads to good clinical results in the short term and in the midterm.

The MRI evaluation revealed 32 patients with complete filling of the cartilage lesion. Patients with incomplete filling tended to have a persistent subchondral edema. Although speculative, incomplete filling may be associated with small gaps in the repair tissue or in the bonding area down to the subchondral bone plate and could result in a direct connection to the joint fluid and may provide a persistent stimulus for the subchondral bone.

In our study population, some concomitant surgical procedures such as high tibial osteotomy or patella balancing were performed. We are aware that these procedures may influence the final result, but these interventions were necessary to provide all patients with the same biomechanical requirements and comparable loading of the treated cartilage lesion in the postoperative follow-up. We believe that these interventions—even though resulting in additional scars—lead to a more homogeneous study group compared with a study population in which axial and patella malalignment are not addressed in the treatment. Furthermore, some patients underwent additional microfracture in the secondary lesions. However, the treated lesions were small defects less than 1 cm^2 and concerned only 5 patients. In addition, only a few cases received BioSeed-C by an arthroscopic approach. Therefore, we cannot conclude whether the mode of implantation may have an effect on morbidity or clinical results. Further studies have to elucidate whether arthroscopic or arthrotomic implantation of scaffold-assisted ACI leads to better strength, optimal fixation, and superior clinical outcome.

To get further objective information about the function of the treated knees, we performed biomechanical testing showing statistically significant reduction of maximum strength of the injured leg of the ACI patients. It has previously been shown in various knee disorders that lower muscular strength is associated with a poorer outcome. In particular the fact that quadriceps muscle weakness is considered a primary risk factor of knee joint osteoarthritis leads to the conclusion that strength training and a consequent rehabilitation process are crucially important in patients with cartilage damage of the knee.[44] One of the aims of this study therefore was to objectively assess muscular strength capacities in our patients after standardized cartilage repair of the knee. To our knowledge, this is the first study showing remarkable strength deficits at midterm follow-up after scaffold-assisted ACI. The only other available study including isokinetic measurements of ACI patients is the recently published study by Loken et al,[26] where 21 patients were evaluated isokinetically 1, 2, and 7.4 years after first-generation ACI. They also found highly significant side-to-side differences for knee flexion and extension strength. Strength deficits of the operated knee decreased from year 1 to year 2 and then remained constant at 7.4 years. Obviously, all tests were performed in their investigation in a concentric mode. In our study, we mainly confirmed the results of Loken et al and additionally assessed strength in eccentric contraction, bearing in mind that this is the mode that requires more coordination in more demanding situations so that strength deficits

might be more pronounced. The strength deficit was greater in knee extension than in knee flexion, but also the healthy leg was affected by the muscular weakness. Müller et al[33] reported mean peak torque values of about 160 N·m for concentric and 200 N·m for eccentric knee extension using the same dynamometer and the same setting. For knee flexion, the average peak torque in healthy knees in their study was 115 N·m for concentric and 150 N·m for eccentric contraction. These values are far higher than the values measured in our study and suggest that patients 4 years after ACI suffer from quadriceps and hamstring weakness that is more obvious on the operated side and for knee extensors but also present in the nonoperated knee and in knee flexors.

Because our study lacks preoperative isokinetic data, it cannot be concluded from the results of this study whether the measured deficits are due to muscular atrophy, functional/neuromuscular impairments, or an underlying preoperative weakness. A preexisting deficit, though, is highly supposable considering the low values of the KOOS Sports/rec and Noyes score preoperatively, indicating that obviously pain prevented the patients from participating in sports activities. Additionally, various studies showed that proprioception is altered in injured knees and after knee joint surgery,[2,5-7,11] suggesting that also neuromuscular coordination (eg, coordinated muscle fiber innervation and recruitment) is disturbed in ACI patients. This problem of soft tissue damage and invasive surgery could be resolved with improved mini-open and arthroscopic techniques for cell implantation. Finally, it can be assumed that maximum strength training is inadequately performed in ACI rehabilitation, leading to a persistent muscular atrophy and weakness. These hypotheses should be addressed in further studies including preoperative strength measurements as well as objective assessment of proprioception.

Another reason for the persistent quadriceps weakness could be the short period of postoperative treatment under the guidance of a physical therapist, which was limited to a maximum of 6 months. After this period, the patients trained on their own and the training as well as its intensity were no longer controlled by a specialist. However, tissue remodeling and cartilage regeneration takes years after implantation.[25] Therefore, for future treatment, we suggest a more detailed rehabilitation program over 2 years with continuous monitoring and repetitive patient checks with special emphasis on the quadriceps force and specified patient instructions. In summary, the present results underline the importance of a postoperative rehabilitation plan with restoration of muscular strength and proprioception after ACI. Strength training should begin preoperatively and should be performed as far as pain can be tolerated and healing of the transplant is not jeopardized.

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