Characterized Chondrocyte Implantation in the Patellofemoral Joint : An Up to 4-Year Follow-up of a Prospective Cohort of 38 Patients

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Characterized Chondrocyte Implantation in the Patellofemoral Joint

An Up to 4-Year Follow-up of a Prospective Cohort of 38 Patients

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Background: Autologous chondrocyte implantation (ACI) is an accepted treatment option for selected condylar cartilage defects in the knee. Results for patellofemoral chondral defects have been less favorable.

Hypothesis: Autologous chondrocyte implantation with characterized chondrocytes will result in clinically relevant improvement in patellofemoral lesions.

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

Methods: Patients with symptomatic patellofemoral full-thickness cartilage lesions were treated with ACI using characterized chondrocytes (ChondroCelect) covered with a collagen type I membrane. Clinical outcome was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and a visual analog scale (VAS) for pain. Responders were defined using 5 categories ($\geq$10 points and $\geq$20%, 30%, 50%, 70%) based on the KOOS and VAS. Treatment failure was defined as partial loosening of more than 20% of the graft with subsequent procedures to the subchondral bone.

Results: Thirty-eight patients, with a mean defect size of 4.89 cm^2 (range, 1.5-11 cm^2), were treated for a patellar defect (n = 28), trochlear defect (n = 7), or a kissing lesion (trochlea and patella; n = 3). The minimum follow-up period was 24 months (mean, 37 months; range, 24-72 months). Treated patients showed statistically significant improvements in the KOOS (at 12, 18, 24, 36, and 48 months) and VAS (at the same time points) compared with pretreatment for each time point. Responder analysis identified approximately 84% of patients with a clinically relevant improvement greater than 10 points at 3 years. Treatment failure was observed in 5 patients. The most commonly reported adverse events were joint crepitation (n = 18) and arthrofibrosis (n = 7). No relationship could be found between clinical outcome and anatomic characteristics of the patellofemoral joint, lesion size and site, time since onset, or age. Nine patients required additional surgery: 6 because of persistent symptoms and 3 for hardware removal.

Conclusion: Characterized chondrocyte implantation resulted in statistically significant and clinically relevant improvement over time. These results add to the evidence demonstrating that ACI is a valuable cartilage repair technique for patellofemoral lesions.

Keywords: autologous chondrocyte implantation (ACI); characterized chondrocyte implantation (CCI); patellofemoral lesions; cartilage repair

Patellofemoral lesions, caused by trauma, osteochondritis dissecans, patellofemoral malalignment, and chondromalacia, result in anterior knee pain. Their treatment remains a challenge. As in the tibiofemoral joint, these chondral lesions may arise from both macrotrauma and repetitive microtrauma. Additionally, there are anatomic factors that specifically contribute to patellofemoral cartilage damage, such as patella alta, an increased Q angle, a dysplastic trochlear groove, and soft tissue problems (such as a weakened or hypoplastic vastus medialis oblique muscle or a contracted lateral retinaculum).[1,16,47]

Focal cartilage lesions, particularly those with a diameter greater than a few millimeters, show little tendency to heal spontaneously.[8] Reported occurrence of patellofemoral cartilage lesions during arthroscopy varies, with Curl et al[12] reporting 25% and Widuchowski et al[62] reporting figures of up to 40% of all diagnosed cartilage lesions. In a study of articular cartilage defects in 1000 knee arthroscopies, Hjelle et al[29] reported that 11% of the focal chondral or osteochondral defects were located in the patella and 6% were located in the trochlea; Aroen et al[3] reported 8% were located in the trochlea and 23% in the patella.

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The persistence of untreated focal chondral lesions is considered a risk factor for the development of more extensive joint damage, which finally leads to frank osteoarthritis.[38,48] Restoration of normal, long-term, and pain-free motion of the joint requires cartilage repair preferentially with a structure, mechanical properties, and durability of natural articular cartilage.[11,26,31,52] Therefore, a number of interventions intended to re-establish the cartilage surface, including mosaicplasty, marrow stimulation techniques (eg, microfracture, abrasion arthroplasty, or drilling), massive allograft implantation, and autologous chondrocyte implantation (ACI), have been developed.[5,23,32,33,44,57]

Mosaicplasty, developed in the early 1990s by Hangody et al,[22] uses multiple cylindrical osteochondral autograft plugs harvested from the minimal weightbearing periphery of the femoral condyles, with subsequent transplantation into the defect area. Good results have been published using this technique; however, its use is restricted to smaller lesions because of the limited availability of donor plugs.[4,23] Hangody et al report up to 84% good and excellent clinical results in the patella.[22] Bentley et al[4] were much less optimistic with this technique and described only 60% good and excellent results.

The marrow stimulation technique of microfracture is frequently used as a first-line treatment for articular cartilage defects of the knee and results in significant functional improvements within the first 2 years after treatment; this arthroscopic procedure promotes cartilage repair by penetrating the subchondral bone and stimulating the formation of a blood clot, leading to mostly fibrocartilage formation.[7,36,42] However, fibrocartilage is considered less durable and mechanically inferior to the original articular cartilage and can degenerate over time, leading to a return of clinical symptoms.[9,26,31,41,42] One article states that microfracture is not a durable treatment for the patella but does not specify results.[58]

Massive allograft implantation is mostly used as a salvage technique in young patients with severe articular cartilage disease, in this case of the patella with outcomes comparable with the other techniques. If incorporation occurs adequately, it shows the same improvements in pain and function with a low risk of osteoarthritis progression.[32]

Autologous chondrocyte implantation with a periosteal flap was first described by Brittberg et al as a procedure for the successful repair of focal cartilage lesions with hyaline-like repair tissue, although most studies reported the formation of fibrocartilage or mixed hyaline/fibrocartilage.[4,5,30,34,47] Since the advent of other scaffolds and less invasive techniques, it is now considered a more acceptable treatment option, with more than 12,000 patients treated as of 2006.[21,35,55] Numerous studies report the success of ACI in treating full-thickness cartilage lesions in the femoral condyles of the knee, but the treatment of patellar defects appears more challenging with less favorable results. However, recent reports show an increased success rate with patellar defects, attributable to the combined correction of patellar maltracking and trochlear dysplasia.[25,39,40] Although several recent articles on the subject stress the importance of the concomitant correction of anatomic or physiological abnormalities, there are no clear indications as to which features of the patellofemoral joint could be predictive of outcome in these patients.

This prospective case study aimed at assessing the clinical outcome in patients with patellar defects after treatment with autologous characterized chondrocyte implantation (CCI), the only advanced therapy medicinal product (ATMP) approved so far by the European Medicines Agency. The CCI treatment was developed to ensure consistent and reproducible cartilage formation in vivo with a pharmaceutically safe product. A secondary objective was an exploration of anatomic features of the patellofemoral joint and their possible influence on clinical outcome.

MATERIALS AND METHODS

Patient Characteristics and Clinical Outcome Assessments

Eligible patients aged between 18 and 50 years were included in a prospective cohort study for the treatment of focal cartilage defects with characterized chondrocytes (ChondroCelect, TiGenix NV, Haasrode, Belgium) in the patella, trochlear groove, or "kissing lesions" on both the trochlea and patella. They were elected for surgery because extensive nonoperative treatment for pain and function with physical therapy failed. Patients were included between 2003 and 2008 (see Results). All isolated cartilage defects were classified as International Cartilage Repair Society grade III or IV.[6] An additional realignment procedure was performed if there was a clinical patellofemoral malalignment. All patients had a routine series of radiographs (including anteroposterior view, lateral view, skyline view, and full-leg standing view), and all knees were preoperatively assessed by magnetic resonance imaging (MRI) and/or computed tomography-arthrography. Furthermore, MRI was used for the subsequent monitoring of cartilage repair tissue at 12 and 24 to 36 months after CCI. Two musculoskeletal radiologists independently assessed MRI scans using 8 of 9 magnetic resonance observation of cartilage repair tissue (MOCART) criteria, excluding signal intensity because of a lack of adequate

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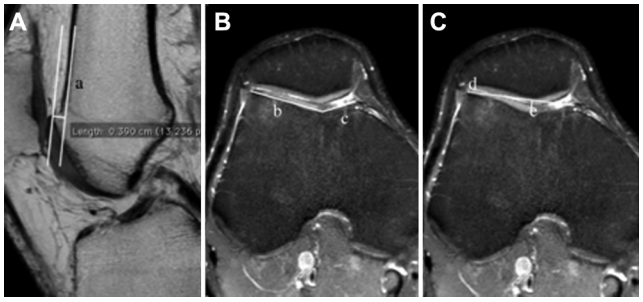

Figure 1. (A) a = Ventral prominence. (B) Facet asymmetry. Angle between b and c = 100% sulcus angle. (C) e = Trochlear depth (line perpendicular to d connecting the border of the medial and lateral trochlea).

sequences.[37] Subsequent analyses were done on MRI pertaining to the shape of the patellofemoral joint: height (Caton-Deschamps index) and shape of the patella, lesion site on the patella according to Fulkerson, and other characteristics such as depth of the trochlea, lateral facet asymmetry, presence of a superior bump or nipple, and sulcus angle[18,49,59] (Figure 1). The Knee Injury and Osteoarthritis Outcome Score (KOOS) and visual analog scale (VAS) for pain were used to assess clinical outcome.[53] All patients were asked to complete a VAS and KOOS questionnaire for the afflicted knee (preoperatively and at 6, 12, 18, 24, 36, 48, and 60 months after surgery).

Adverse events and complications were monitored. Failures were defined as partial loosening of more than 20% of the graft with subsequent procedures to the subchondral bone such as microfracture or curettage. The Ethical Committee of the University Hospitals Leuven approved this study.

Technique and Rehabilitation Protocol

ChondroCelect (TiGenix NV) is an advanced cell therapy product (the first one approved according to the European regulatory framework for ATMPs), consisting of autologous cartilage cells that are expanded ex vivo through a controlled and consistent manufacturing process aimed at maintaining the cells' ability to maximally conserve their preculture phenotype and high quality cartilage-forming capacity.[13-15]

Characterized chondrocyte implantation was performed by a standardized 2-stage technique for cartilage harvesting and surgical implantation. In brief, an autologous cartilage biopsy was harvested from the nonweightbearing area of the femoral condylar periphery during the first arthroscopic assessment. Under sterile and temperature-controlled (2°C-8°C) conditions, the tissue was shipped to the Cell Expansion Facility (TiGenix NV) within 48 hours after arthroscopic harvest. The chondrocytes were enzymatically released from the harvested cartilage and expanded in vitro during 4 to 6 weeks.[56]

The characterized chondrocytes were implanted via arthrotomy 4 to 6 weeks after the initial biopsy, using a minimally invasive lateral arthrotomy with a Z-plasty of the lateral retinaculum if the lesions were located laterally and tilt

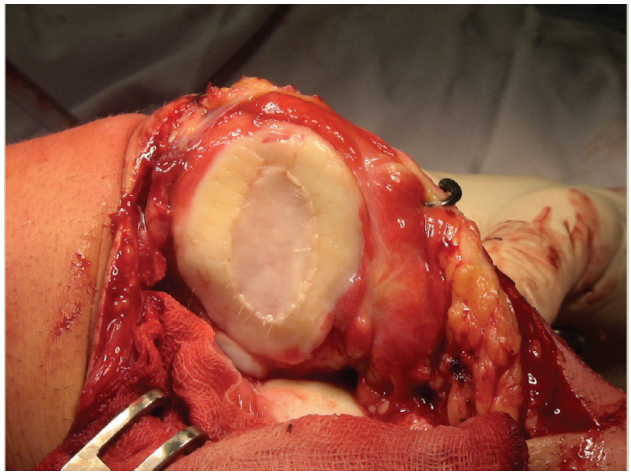

Figure 2. Large cartilage defect after suturing the membrane to the surrounding stable cartilage margin.

was present; for medial lesions, a standard medial approach was used. The cartilage defect was thoroughly debrided to obtain an intact, stable margin around the defect (maintaining the calcified cartilage layer when possible). A bilayered collagen membrane (Chondro-Gide, Geistlich Biomaterials, Wolhusen, Switzerland) was sutured over the lesion to obtain a watertight seal; the cultured chondrocytes were injected underneath this membrane, and a final suture closed the seal (Figure 2). The total number of administered cells depended on the size of the cartilage defect; a dose of 0.8 to 1 million cells/cm^2 was used. Fibrin glue was sprayed over the flap. The lateral arthrotomy was closed capsule to synovium to serve as a lateral retinacular release. Additional realignment and stabilization procedures (anteromedialization of the tibial tubercle according to Fulkerson, a Roux-Goldthwait procedure, and Insall medial imbrication) were performed on clinical indication.[18,54]

After surgery, all patients received a customized rehabilitation protocol. In the first postoperative weeks, protecting the healing tissue from load and shear forces was emphasized, thus allowing maximal cell adherence and engraftment and preventing intra-articular adhesions. Immediate progression to full weightbearing in extension was allowed, although mobilization to 90° of knee flexion was permitted at 4 weeks after surgery, and a gradual return to full range of motion was allowed after 6 to 8 weeks. During the first weeks, strength and functional training were focused on neuromuscular control, proprioception, and coordination. After 2 to 6 weeks, closed chain exercises were gradually introduced, with increasing load and volume between 3 to 6 months. Impact training and sport-specific training were allowed around 10 to 12 months, depending on the level and type of sport and under strict medical supervision.

Statistical Analysis

The KOOS questionnaires were completed preoperatively at baseline and various time points thereafter; the nominal

posttreatment collection times were 6, 12, 18, 24, 36, 48, and 60 months. The sports domain score was missing at a substantial number of time points, and consequently, this domain was excluded from the calculation of the overall KOOS (ie, the mean of the remaining 4 KOOS subdomains). The VAS for pain data were collected for both the untreated and treated knees at baseline and at the same nominal time points. The results were analyzed using descriptive statistics and confidence intervals. The KOOS-based responder analysis defined responders as patients with a change from baseline exceeding 10 points and 20%, 30%, 50%, and 70% (the change from baseline was calculated as a relative change: ie, 100 × (score – baseline)/baseline). The VAS-based responder analysis defined responders as patients with a score that was reduced from baseline by 12 points according to the validated definition of a "minimally meaningful clinical difference" (MMCD).[34] Mann-Whitney *U* (and Kruskal-Wallis) tests as well as Fisher exact tests were used to compare groups. Spearman correlations were used to study the association between variables. All analyses were performed using SAS software for Windows, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

Between 2003 and 2008, a total of 38 consecutive patients (12 [32%] male and 26 [68%] female) were included in the study, with lesions located in the patella (n = 30, 28 patients), trochlear groove (n = 7, 7 patients), or kissing lesions (n = 3, 3 patients); mean cartilage lesion size was 4.89 cm^2 (range, 1.5-11.0 cm^2). No patients were lost to follow-up. One patient who had both patellae treated at the same time was excluded from the clinical assessment. For 1 patient who had the other patella treated at 1 year and 1 patient who had the patella treated at 2 years, KOOS data after the operation of the second patella were excluded from analysis because the KOOS was not filled out per lesion but per patient. The mean age of the patients was 30.9 years (range, 14-49 years), and minimum follow-up after surgery was 24 months (mean, 39 months; range, 24-72 months). All patients except 6 had 1 to 4 previous surgeries for their condition, ranging from lateral release with arthroscopic debridement to microfracture and realignment. Fifteen patients had 1 previous surgery, 9 had 2, 4 had 3, and 4 had 4. Fifteen patients had a previous or concomitant procedure because of malalignment; 12 patients underwent a Fulkerson procedure at the moment of implantation, 1 patient had previously undergone a Roux-Goldthwait procedure, and 2 patients had previously undergone a Fulkerson procedure.[18,54] Mean time since onset was 7.73 years (range, 0.16-30 years). No major medical or surgical complications were observed in the perioperative and immediate postoperative period (Table 1).

Treatment failure (requirement for reintervention of loosening of more than 20% of the repair with additional subsequent procedures to the subchondral bone) was observed in 5 patients. The time to failure was always more than 1 year after the CCI (Figure 3). The youngest patient had a total patellectomy, 2 of 5 patients with treatment failure subsequently had a patellofemoral arthroplasty, and 2 underwent a total knee arthroplasty. All patients with treatment failure showed good filling of the defect on MRI at 1 year, but with subsequent and complete loosening of the repair tissue. The earliest failure was at 18 months, followed closely by 2 patients at 19 and 23 months; 2 more patients failed at 27 and 50 months (Kaplan-Meier plot for time to failure in Figure 3). All treatment failures occurred in patients with persisting symptoms since more than 7 years: 4 were patellar cartilage lesions, and 1 was a kissing lesion. In the 4 patella failures, the whole patella was resurfaced with lesion sizes greater than 7 cm^2.

TABLE 1
Patient Characteristics

Patients, n (male/female)	38 (12/26)
Lesion site, n	
Patella	30
Trochlea	7
Kissing	3
Lesion size, mean (range), cm^2	4.89 (1.5-11)
Age, mean (range), y	30.9 (14-49)
Previous surgeries, n	
0	6
1	15
2	9
3+	8
Fulkerson procedures, n	15 (12 concomitant, 3 previous)
Years since onset, mean (range)	7.73 (0.16-30)

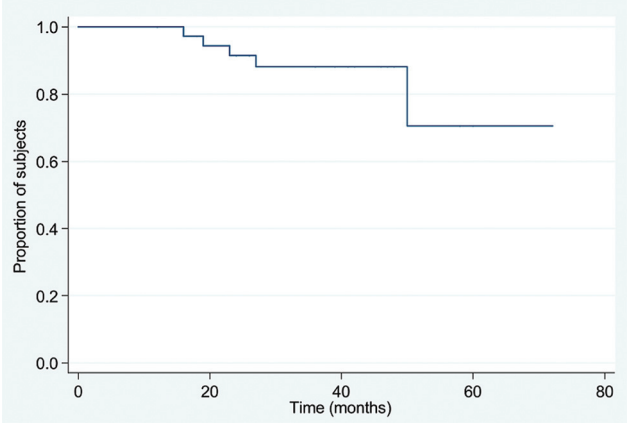

Figure 3. Time to treatment failure.

KOOS and VAS for Pain

The mean overall KOOS (Table 2) at baseline was 47.9. The mean overall KOOS ± standard deviation increased to 64.2 at 6 months, after which it varied between 68.4 ± 16.8 at 12 months and 73.6 ± 19.1 at 48 months. At all postbaseline

TABLE 2
Summary Statistics for Overall KOOS: Change From Baseline[a]

Months	n	Mean	SD	Min	Median	Max	CI, Lower	CI, Upper	*P* Value	Absolute Value
0	—	—	—	—	—	—	—	—	—	47.9
3	27	14.6	17.6	–16.9	13.9	48.7	7.7	21.6	—	64.0
6	26	17.2	16.3	–20.3	20.5	48.1	10.6	23.7	—	67.2
9	23	19.8	18.2	–4.0	19.6	51.9	11.7	27.4	—	69.2
12	29	18.8	13.8	–2.8	22.5	43.4	13.6	24.1	.0001	68.4
18	28	22.0	18.3	–8.1	19.6	53.2	14.9	29.1	.0001	70.4
24	25	21.5	16.4	–6.6	17.9	50.9	14.8	28.3	.0001	70.5
36	22	22.3	16.8	–3.5	17.9	57.5	14.9	29.8	.0001	69.4
48	14	26.2	20.9	1.5	25.0	63.4	14.1	38.2	.0001	73.6

[a]Absolute values added in the last column. KOOS, Knee Injury and Osteoarthritis Outcome Score; SD, standard deviation; Min, minimum; Max, maximum; CI, confidence interval.

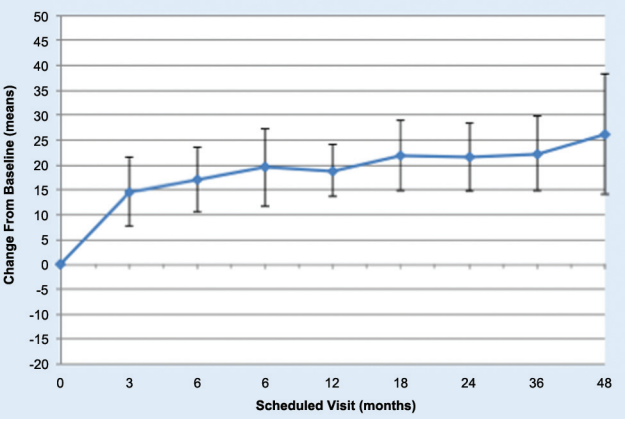

Figure 4. Change in overall Knee Injury and Osteoarthritis Outcome Score from baseline to 48 months.

time points, the 95% confidence interval (CI) for the change from baseline excluded zero, demonstrating a statistically significant change in overall KOOS from baseline. From month 6 to month 48, the lower limit of the CI exceeded 10 points (Table 2 [CIs included] and Figure 4 [CIs not included]).

As shown in Figure 4, the mean overall KOOS showed a marked increase at 3 months and, from there, a gradual upward trend until month 48. The individual KOOS domains increased in a similar way. The quality of life domain had much lower initial values and showed the greatest improvement from baseline. Except for the sports domain, the 95% CI always excluded zero from month 12 to month 48 (Table 3 and Figure 5). The KOOS for the contralateral knee was not collected.

The mean VAS for pain score for the treated knee was 62.1 at baseline, falling to 29.5 (CI, –43.5 to –22.3) at 3 months and then varying between 33.7 (CI, –44.5 to –16.2) at month 6 and 27.4 (CI, –58.3 to –12.1) at month 48. The VAS for the contralateral knee did not change but was never asymptomatic.

Responder analysis according to the OMERACT-OARSI responder criteria[50,51] (Table 4) showed an improvement in the overall KOOS over time. When compared with baseline, an improvement of more than 10 points in the overall KOOS from baseline at 12, 24, 36, and 48 months was seen in 72%, 81%, 84%, and 64% of patients, respectively. An improvement of more than 20% in the overall KOOS from baseline at 12, 24, 36, and 48 months was seen in 72%, 84%, 73%, and 64% of patients, respectively. An improvement of more than 50% was seen in half of the patients after 4 years. An MMCD of 12 of 100 on the VAS for pain at 12, 24, 36, and 48 months was seen in 71%, 74%, 79%, and 70% of patients, respectively.

No statistical and clinical difference could be found between patients with or without realignment. No statistical difference in clinical outcome could be found between patients with lesions on the lateral side compared with central lesions or medial lesions (see the Appendix, available online at http://ajs.sagepub.com/supplemental/).

Imaging

The MRI scans were available for 34 patients at the 2- to 4-year follow-up. Hypertrophic filling of the defect was seen in 10 of 31 patients; 4 of 31 patients had mechanical complaints, necessitating an arthroscopic intervention. Complete filling of the defect was seen in 10 patients. Nine patients had a filling of more than 50% of the adjacent cartilage, and 1 patient had a filling of less than 50% (Figure 6). One patient had no complaints but an exposed subchondral bone on the medial site of the patellar defect. The structure of the repair tissue in most patients (n = 27) was inhomogeneous. Repair tissue was fully integrated basally and laterally with the adjacent cartilage in 16 patients.

At no time point were any relations found between anatomic features on MRI and patient-reported clinical outcome. No relations were found between the morphological characteristics of the patellofemoral joint and the lesion characteristics or locations. The lesion size of the central lesions was statistically larger than the other lesions.

In all patients, the Caton-Deschamps index was measured on the section with the longest proximodistal length of the patella and the patellar tendon under tension, as MRI scans were taken slightly flexed.[10] Eleven of the 12 concomitant Fulkerson osteotomies were measured preoperatively and postoperatively, showing a statistically

TABLE 3
Confidence Intervals for KOOS Subscores: Change From Baseline[a]

Months	Pain	Symptoms	Activities of Daily Living	Sports	Quality of Life
0	52.7	56.5	59.9	34.3	23.3
12	14.5 to 29.3	10.2 to 21.5	10.0 to 23.8	3.5 to 31.8	13.3 to 27.8
18	14.0 to 32.3	11.3 to 27.5	10.7 to 28.1	5.0 to 31.1	18.5 to 32.3
24	11.6 to 30.4	12.4 to 26.7	8.7 to 26.0	1.4 to 37.0	20.9 to 33.7
36	13.0 to 32.8	8.9 to 25.9	13.0 to 31.3	–9.0 to 33.1	18.1 to 34.1
48	14.1 to 44.2	6.9 to 27.8	4.7 to 36.8	–0.2 to 57.7	21.8 to 45.3

[a]Absolute values are shown in the first row. All are highly significant except sports at 36 and 48 months. KOOS, Knee Injury and Osteoarthritis Outcome Score.

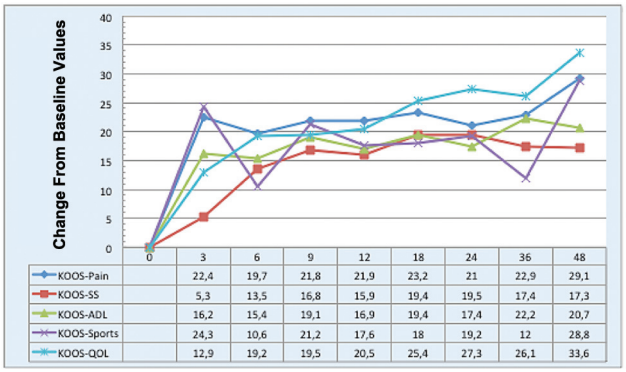

Figure 5. Change from baseline in different domains of the Knee Injury and Osteoarthritis Outcome Score (KOOS) over time.

significant difference in the index: 1.1 preoperatively versus 0.94 postoperatively (P = .002, Wilcoxon signed-rank test).

Safety

In total, 29 patients reported adverse events. The most commonly reported adverse events were arthralgia (n = 18), joint crepitation (n = 18), and arthrofibrosis (n = 7). Seven (19.4%) patients had to be manipulated under anesthesia because of arthrofibrosis. After manipulation, these patients regained full range of motion. Nine (25.0%) patients underwent an arthroscopy, 6 of these 9 because of a persisting symptomatic click or residual patellofemoral joint pain; 4 of these 6 (11.1%) patients were found to have hypertrophic tissue that caused the click, and another 2 (5.6%) patients had a partial loosening less than 20% of the repair tissue. In 3 (8.3%) of these 9 patients, a second-look arthroscopy without clinical indication was performed at the moment of removal of hardware, but no biopsy specimens were obtained because no consent to do so was given.

DISCUSSION

This prospective cohort of patients with large (mean lesion size, 4.89 cm^2) patellofemoral cartilage lesions treated with CCI showed statistically significant improvements based on the VAS and KOOS. Although there are a number of studies showing varied outcome after ACI as treatment for patellofemoral lesions, this is the first report demonstrating the efficacy of CCI in this context. The lesion size in this prospective cohort of patients corresponds well to the lesion sizes of the different articles cited below, except for the Henderson articles,[26,28] with a mean lesion size of 3 cm^2.

In an early pilot study on ACI as a treatment for cartilage lesions in the knee, Brittberg et al[5] reported somewhat disappointing results for a subgroup of patients with patellofemoral lesions, with only 2 of 7 treated patients (28.6%) showing a good or excellent result. However, more recent reports have indicated better results after treatment of patellofemoral cartilage lesions with ACI. Peterson et al[46] published long-term data on 61 patients with cartilage defects in the femoral condyle or patella and reported good to excellent results in 76% of patients after ACI combined with realignment when required. In addition, Minas and Bryant[40] reported data on ACI in 8 isolated patellar lesions, 9 isolated trochlear lesions, and 4 patellotrochlear "kissing lesions," with improved quality of life and 71% of patients rating their outcome as good or excellent. Gobbi et al[20] used a biodegradable hyaluronan-based scaffold seeded with autologous chondrocytes as treatment for patients with lesions in the patella (n = 22) and trochlea (n = 10) and reported objective improvement based on the International Knee Documentation Committee A or B at 24 months (29 of 32, 90.7%) compared with baseline (6 of 32, 18.8%). Niemeyer et al[43] excluded patients with patellofemoral malalignment from their study to create a homogeneous patient group with patellar cartilage defects; good to excellent results were reported in 70% of the patients. In contrast, Gigante et al[19] excluded patients without patellofemoral malalignment and performed a Fulkerson procedure in all patients, with 36-month data from a patient satisfaction survey reported as good to excellent in 93% of patients. Henderson and Lavigne[28] compared patients with and without patellofemoral malalignment and reported good to excellent outcomes on a Cincinnati scale in 86% of patients treated with ACI combined with distal or proximal realignment and in 55% of patients treated with ACI alone without patellofemoral malalignment. They stated that depending on the lesion site, even patients with normal alignment could benefit from unloading the patellofemoral joint to maximize the result obtained.[28]

TABLE 4
Improvement in KOOS From Baseline[a]

	Improvement in KOOS					
Months	>10 Points	>20%	>30%	>50%	>70%	MMCD ≥12 Points on VAS
12	21/29 (72)	21/29 (72)	16/29 (55)	14/29 (48)	9/29 (31)	22/31 (71)
24	20/25 (81)	21/25 (84)	13/25 (52)	11/25 (44)	7/25 (28)	20/28 (74)
36	19/22 (84)	16/22 (73)	13/22 (59)	9/22 (40)	7/22 (32)	19/25 (79)
48	9/14 (64)	9/14 (64)	7/14 (50)	7/14 (50)	7/14 (50)	7/10 (70)

[a]Based on a 5-category responder analysis according to OMERACT-OARSI and 12-point minimally meaningful clinical difference (MMCD) on visual analog scale (VAS) for pain. Values are shown as number of patients/total number of respondents (%). KOOS, Knee Injury and Osteoarthritis Outcome Score.

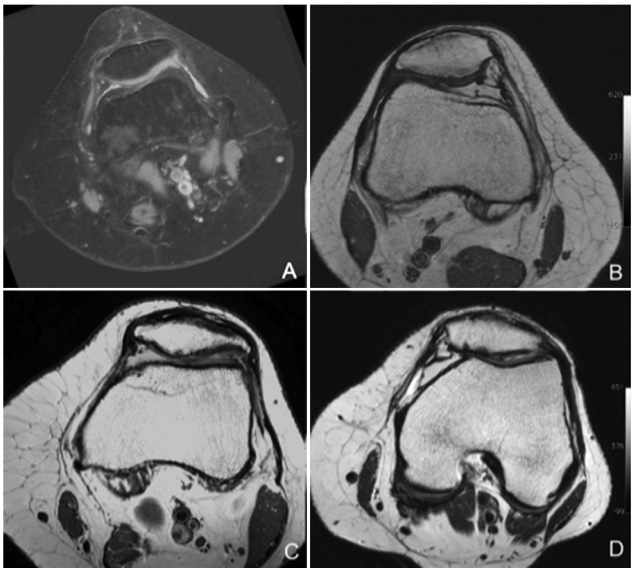

Figure 6. (A) Complete filling of a patellar defect. (B) More than 50% filling of a patellar defect. (C) Less than 50% filling of a patellar defect. (D) Exposed bone.

Vasiliadis et al,[61] in a very recent article on patellofemoral cartilage lesions and multiple lesions including patellofemoral lesions, treated by Lars Peterson, showed very nice long-term results in 3 of 4 of these patients, provided all concomitant factors were taken care of as well. Niemeyer et al,[43] in a recent article, looked at anatomic features that could be of interest in the treatment of patellofemoral cartilage lesions and found that Fulkerson type 2 lesions (lesions on the lateral facet) responded in general better to treatment than did medial lesions or complete lesions in a multicenter prospective case series of 75 patients. We could not corroborate these findings in our group of 28 patellar lesions.

The only interesting finding in our study when looking at the anatomy of the patellofemoral joint was the fact that a Fulkerson osteotomy statistically significantly lowered the Caton-Deschamps index (from 1.10 to 0.94; P = .002), meaning that the osteotomy itself induces a distalization of the patella, unloading the distal part even more, so there may be no need to additionally distalize the patella when doing this type of osteotomy. Although the above-mentioned prospective case series varied in study design, our results show consistency with recent reports and add to the body of evidence demonstrating ACI to be a useful technique for the repair of patellofemoral cartilage lesions. It is also important to note that, with the exception of 6 patients, all patients included in our study had undergone several previous surgeries to treat their symptomatic patellofemoral cartilage defect and thus underwent CCI as a salvage procedure after failed attempts to relieve the complaints by using other operative techniques (eg, debridement, microfracture, or lateral release).

Furthermore, our study is not only the first to report on CCI as a treatment for patellofemoral lesions, but it is also the first to report on the outcome of ACI in patients with patellofemoral lesions using responder criteria based on the KOOS, which is comparable with the OARSI responder criteria.[50,51] The KOOS is considered to be the best validated clinical and functional patient-reported outcome measure for use after cartilage repair, with an increase of 10 points in the KOOS considered to be clinically relevant.[53] The most dramatic improvement was seen in the quality of life part, the most sensitive item in the KOOS, with 93% of patients showing an improvement of more than 30% even at 48 months. In comparison with reference data for the KOOS in a normal population, however, the absolute values of the different KOOS items remain lower, indicating that a lot of these knees remain symptomatic.[45] In general, the situation in daily life becomes acceptable for patients, as indicated by the quality of life part of the KOOS.

In this study, no unexpected safety issues were encountered. Seven patients needed manipulation under anesthesia probably because of a rather restrictive rehabilitation protocol, especially in lesions on the distal pole of the patella, although we could not find a relationship between distal pole lesions and manipulation under anesthesia. In 6 of 38 patients, a re-arthroscopy was performed for loosening (n = 2) or hypertrophy (n = 4); this rather low number of reinterventions for this reason in comparison with the Henderson articles, which reported a reoperation rate of 52%, could be because of the use of a collagen membrane instead of a periosteal flap, as Henderson et al state that the majority of reinterventions were related to its use.[27,28]

We had 5 treatment failures, all occurring in lesions on the patella that were large (>7 cm^2) and all in women with more than 7 years of complaints. This is in accordance with the randomized trial done with the same product, where treatment failure was also associated with female gender.[60] Usually, treatment results are less good when lesions are larger, as shown by Niemeyer et al,[43] which is in accordance with our group of failures in large lesions, but on the other hand, we could not find a relation between the KOOS and lesion size.

The most important limitations of this study are the patient mix and the lack of a control group. In this group, trochlear, patellar, and kissing lesions were grouped, as separate analysis on the trochlea and the kissing lesions would not yield any relevant data because the separate groups were too small. The lesion size ranged from 1.5 cm^2 to 11 cm^2.

In addition, concomitant realignment procedures may have affected the outcome. Henderson and Lavigne[28] showed, in their study comparing realigned versus nonrealigned patellofemoral joints, that unloading the patellofemoral joint acted to optimize the outcome. In our study, on the contrary, we could not confirm this finding. Realignment without addressing the cartilage lesion was not looked at because this study was not a comparative study, but as Minas and Bryant[40] stated in their article on the role of ACI in the patellofemoral joint, the results of realigning without additional cartilage treatment are good in lateral and distal lesions, and this has been confirmed by Henderson and Francisco as well.[24]

In this study, biopsy taking during second-look arthroscopy was not done, so no information can be given on the quality of the repair tissue. On the other hand, these data would again be mere case reports on a few patients.

In view of recent discussions on the relevance of controlled patient trials to general clinical practice,[17] a review of available publications on patellofemoral cartilage lesions and the varied clinical outcomes after treatment with ACI with and without correction of malalignment shows that the group of patients included in our study is representative of the patient population that the orthopaedic community is confronted with in the real-life clinical setting. To be able to look for predictors of response and treatment prognosis, a well-performed prospective case study is at least as valuable as a randomized controlled trial, where one looks for a very specific comparison instead of longer term prognostic factors. As such, determining the contribution of malalignment correction to symptom relief remains difficult, and treatment for patellofemoral lesions may have to be regarded as "à la carte," the specifics of which will be selected based on the assessment of the anatomic characteristics of the patellofemoral joint: the medial and lateral soft tissue restraints, muscle balance, trochlear shape, lesion site and size, extensor mechanism alignment, and rotational alignment. One needs to look at the whole picture.[2]

From our additional analyses looking at anatomic features of the patellofemoral joint, the lesion itself, age, gender, time since onset, previous surgery, and early-onset versus long-standing abnormalities, we were not able to discern properties that would indicate a potential positive or negative predictor for results in this patient group. In conclusion, our study showed statistically significant and clinically relevant improvement in patient outcomes after treatment of patellofemoral cartilage lesions with CCI combined with concomitant treatment of accompanying malalignment when necessary.

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