Arthroscopic Second-Generation Autologous Chondrocyte Implantation Compared With Microfracture for Chondral Lesions of the Knee

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Arthroscopic Second-Generation Autologous Chondrocyte Implantation Compared With Microfracture for Chondral Lesions of the Knee

Prospective Nonrandomized Study at 5 Years

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Background: Various approaches have been proposed to treat articular cartilage lesions, which are plagued by inherent limited healing potential.

Purpose: To compare the clinical outcome of patients treated with second-generation autologous chondrocyte implantation implants with those treated with the microfracture repair technique at 5-year follow-up.

Study Design: Cohort study; Level of evidence, 2.

Methods: Eighty active patients (mean age, 29.8 years) and grade III to IV cartilage lesions of the femoral condyles or trochlea were treated with arthroscopic second-generation autologous chondrocyte implantation Hyalograft C or microfracture (40 patients per group). Patients achieved a minimum 5-year follow-up and were prospectively evaluated.

Results: Both groups showed statistically significant improvement of all clinical scores from preoperative interval to 5-year follow-up. There was a significant improvement for the International Knee Documentation Committee subjective score from preoperative to 5-year follow-up (Wilcoxon test, $P < .001$). In the microfracture group, the International Knee Documentation Committee objective score increased from 2.5% normal and nearly normal knees before the operation to 75% normal and nearly normal knees at 5-year follow-up, and the subjective score increased from 41.1 ± 12.3 preoperatively to 70.2 ± 14.7 at 5-year follow-up. In the group treated with Hyalograft C, the International Knee Documentation Committee objective score increased from 15% normal and nearly normal knees before the operation to 90% normal and nearly normal knees at 5-year follow-up, and its subjective score increased from 40.5 ± 15.2 preoperatively to 80.2 ± 19.1 at 5-year follow-up (Wilcoxon test, $P < .001$). When comparing the groups, better improvement of the International Knee Documentation Committee objective ($P < .001$) and subjective ($P = .003$) scores was observed in the Hyalograft C group at 5-year follow-up. The return to sports at 2 years was similar in both groups and remained stable after 5 years in the Hyalograft C group; it worsened in the microfracture group.

Conclusion: Both methods have shown satisfactory clinical outcome at medium-term follow-up. Better clinical results and sport activity resumption were noted in the group treated with second-generation autologous chondrocyte transplantation.

Keywords: cartilage lesion; second-generation autologous chondrocyte implantation; microfracture; arthroscopy; knee

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Articular cartilage lesions, with their inherent limited healing potential, remain a challenging problem for orthopaedic surgeons. Various techniques, both palliative and reparative, have been used to treat this injury with variable success rates. In recent years, regenerative techniques, such as autologous chondrocyte implantation (ACI), have emerged as a potential therapeutic option. Some studies[4,26] suggest the durability of this treatment, especially at long-term follow-up, because of its ability to produce hyaline-like cartilage that is mechanically and functionally stable, and it allows integration with the adjacent articular surface.

However, despite the favorable clinical results obtained by many authors,[4,20,24,26] the use of classic ACI (first generation) has been associated with several limitations related to the complexity and the morbidity of the surgical procedure, as well as the frequent occurrence of periosteal hypertrophy.[20,25] Some recent randomized studies[11,14] have reported controversial results regarding the better performance of the ACI technique compared with other procedures used for cartilage repair.

To address these problems, second-generation ACI has been developed, and biodegradable polymers as temporary scaffolds for the in vitro growth of living cells and their subsequent transplantation onto the defect have become widely used. One of the most used scaffolds for ACI (HYAFF 11, Fidia Advanced Biopolymers Laboratories, Padova, Italy) is entirely based on the benzylic ester of hyaluronic acid and consists of a network of 20-μm-thick fibers with interstices of variable sizes, which has been demonstrated to be a good physical support to allow cell-cell contacts, cluster formation, and extracellular matrix deposition.[5,9,10] The cells harvested from the patient are expanded and then seeded onto the scaffold to create the tissue-engineered product Hyalograft C. Seeded on the scaffold, the cells are able to redifferentiate and to retain a chondrocytic phenotype even after a long period of in vitro expansion in monolayer culture.[1,9,28]

The clinical use of this 3-dimensional scaffold for autologous chondrocyte culture can overcome some of the difficulties of the classic ACI surgical technique. Hyalograft C was introduced into clinical practice in a number of European countries in 1999 for the treatment of full-thickness cartilage defects.[7,17,22] Hyalograft C constructs can be implanted by pasting directly into the lesion, avoiding suturing to surrounding cartilage and obviating the need for a periosteal flap. The features of this device have also permitted the development of an arthroscopic surgical technique for implantation of autologous chondrocytes on a hyaluronic acid support with the aim of reducing patient morbidity, surgical time, and recovery and complications related to open surgery.[18,19] Results of this new bioengineered approach are promising, but there is no agreement about the effective superiority of second-generation ACI to microfracture.

The purpose of our study is to compare the clinical outcome of the patients treated with second-generation ACI to those treated with the microfracture technique at medium-term (5-year) follow-up.

MATERIALS AND METHODS

Patient Selection

Eighty active patients with grade III to IV cartilaginous lesions on the weightbearing surface of the medial or lateral femoral condyle or trochlea were enrolled in the study between 2000 and 2002. Forty patients treated with Hyalograft C second-generation ACI and 40 with the microfracture technique were prospectively evaluated and followed for a minimum of 5 years. During this period, 43 patients were treated with Hyalograft C and 42 patients with microfracture at our institutions, but 2 and 3 patients were not evaluated at 5-year follow-up in the microfracture and Hyalograft C groups, respectively.

Experienced knee surgeons of 2 orthopaedic centers performed the surgical procedures. The choice of the procedures was determined by health and insurance policy of the institutions; all Hyalograft C procedures were performed in 1 institution and all microfractures in another. We noted no socioeconomic or ethnic differences between the 2 groups. The study was approved by the local ethics committees. Patients were selected according to the following criteria: patients between 16 and 60 years who had clinical symptoms such as knee pain or swelling with grade III to IV chondral lesions of the femoral condyles or trochlea from 1.0 to 5.0 cm^2. The exclusion criteria included chondral lesions greater than 5.0 cm^2 or less than 1.0 cm^2, patella or tibial plateau chondral lesions, diffused arthritis or bipolar ("kissing") lesions, noncorrected knee instability, or axial deviation. Also, patients with infective, tumor, metabolic, and inflammatory pathologic changes were excluded from the study. Definitive diagnosis of chondral lesion and sizing was performed during the arthroscopic procedure. The patients with ACL lesions underwent an associated surgical procedure for ACL reconstruction during the same surgical session with cartilage harvesting or microfracture, so all knee instabilities were corrected during the treatment. All patients gave their consent to participate, complied with the required postoperative rehabilitation regimen, and were consecutively treated and prospectively evaluated.

The male:female ratio was 60:20. The mean age at surgery was 29.8 years. The most common cause of the defect was trauma (56.25% of the cases) followed by microtraumatic-degenerative (38.75% of the cases) and osteochondritis dissecans (5% of the cases). Overall, 67.5% of chondral lesions were situated on the medial condyle, 27.5% on the lateral femoral condyle, and in 4 cases the lesion was located on the trochlea. The mean size of the defects was 2.4 cm^2 (1.4-4.4 cm^2). Eighty-four percent of the patients were well-trained athletes, and 12.5% played sports at a highly competitive level (Table 1).

Twenty-nine patients were treated for isolated chondral lesions (12 in microfracture and 17 in Hyalograft C), whereas in 51 patients (63.75%), associated procedures were performed during the same operation: 36 ACL reconstructions and 39 partial meniscectomies (Table 1). There were no statistically significant differences in associated

TABLE 1
Comparison of the Characteristics of the Lesion and Treatment in 2 Groups[a]

	Microfracture Group	Hyalograft C Group	Significance
Gender, male/female, n	27/13	33/7	NS
Age, y	30.6	29.0	NS
Sport activity, %			
Well trained	82.5	85.0	NS
Competitive	12.5	12.5	NS
Etiology, n			Pearson's χ^2 test, $P = .031$
Traumatic	27	18	
Microtraumatic/degenerative	13	18	
Osteochondritis dissecans	0	4	
Associated surgery, n	28	23	NS
ACL	20	16	NS
Previous surgery, n	10	18	Pearson's χ^2 test, $P = .036$
ACL	2	8	
Debridement	3	6	
Mosaicplasty	—	2	
Defect size (SD), cm^2	2.5 (0.79)	2.2 (0.75)	NS
Location, n			NS
Medial femoral condyle	28	26	
Lateral femoral condyle	10	12	
Trochlea	2	2	

[a]Statistical analysis showed more traumatic cases and less presence of previous surgery in the group treated with microfractures. NS, not significant; ACL, anterior cruciate ligament; SD, standard deviation.

surgery between the 2 groups. Moreover, no significant difference was found between the group treated with second-generation ACI and the group treated with microfracture technique with regard to gender, age (mean, 29 and 30.6 years, respectively), defect size (mean, 2.2 and 2.5 cm^2, respectively), location, and patient activity level (Table 1).

Twenty-eight of the patients (35%) underwent previous knee surgery. These operations included 10 ACL reconstructions, 17 meniscectomies, and 9 cartilage arthroscopic repair operations, such as shaving or debridement and multiple osteochondral grafting (in 2 cases from Hyalograft C group). A statistically significant difference between the 2 groups was noted regarding the previous surgery and cartilage damage mechanism (Table 1). There were more traumatic cases (Pearson's χ^2 test, $P = .031$) and less presence of previous surgery (Pearson's χ^2 test, $P = .036$) in the group treated with microfracture: 47.5% of the patients in the group treated with Hyalograft C underwent previous surgery, including 20% of patients previously treated for cartilage lesions, whereas 25% of the patients in the group treated with microfracture underwent previous surgery, including 7.5% of patients treated for cartilage lesions.

Hyalograft C Surgical Technique

The surgical technique described by Marcacci et al[19] was used. The treatment consists of 2 arthroscopic steps.

The first procedure consisted of a biopsy of healthy cartilage for autologous chondrocyte cell culture. A 150- to 200-mg cartilage biopsy specimen was taken from a non-weightbearing site on the articular surface (intercondylar notch) and sent to the processing center in a serum-free nutritional medium. Chondrocytes were seeded on a hyaluronic acid–based scaffold (Hyaff 11) to obtain the bioengineered tissue Hyalograft C.[17]

After 6 weeks, the second step was performed. All patients in this group were treated arthroscopically. According to the technique developed,[19] a variable diameter (6.5-8.5 mm) delivery device with a sharp edge was used to evaluate the size of the defect to ensure complete coverage of the defect. A circular area with regular margins for graft implantation was prepared with a specially designed cannulated low-profile drill. The delivery device was then filled with a hyaluronic acid patch, which was transported and positioned in the prepared area. The graft was pushed out of the delivery device and precisely positioned within the defect where it remained tightly adhered to the subchondral bone (Figure 1). Because of the physical adhesive characteristics of the graft, no fibrin glue or sutures were used to fix the implant. Under arthroscopic control, the stability of implanted stamps was evaluated during the cyclic bending of the knee.

Microfracture Surgical Technique

The operations were performed according to the technique described by Steadman et al.[30] An initial thorough diagnostic examination of the knee was performed. After identifying the full-thickness chondral lesion, we removed the unstable cartilage, including cartilage loosely attached to the surrounding rim, using a shaver and/or a handheld angled curette (Figure 2). When present, the calcified layer

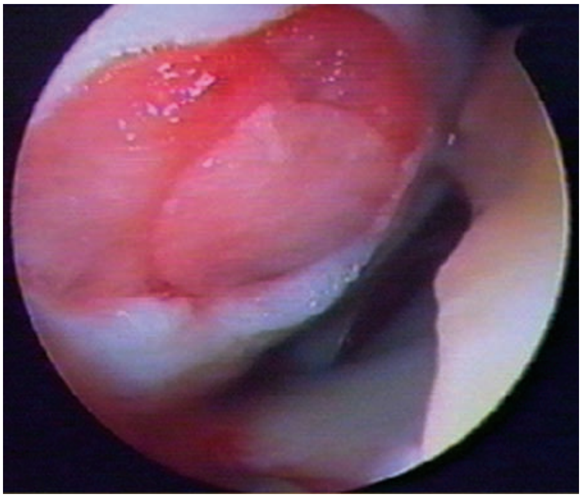

Figure 1. Arthroscopic view of the lesion covered by 3 patches of Hyalograft C.

Figure 2. Arthroscopic view of a grade IV chondral lesion treated with microfractures.

of cartilage was also removed using a curette. Once the exposed subchondral bone plate was thoroughly debrided, we made multiple holes using a Steadman arthroscopic pin. The holes were placed perpendicular to the joint surface, approximately 3 to 4 mm apart and about 2 to 4 mm deep, with care taken not to damage the subchondral plate between the holes. Once the holes were completed, the irrigation fluid pump pressure was lowered to visualize the release of fat droplets and blood from the microfracture holes into the knee. All instruments were then removed. We did not routinely use an intra-articular drain.

Rehabilitation Protocol

The same rehabilitation protocol was used for both treatment groups.

In the early stage (0-6 weeks), the rehabilitation strategies focus on controlling pain, effusion, loss of motion, and muscle atrophy, and the main goal of the treatment was to protect the treated zone by preventing weightbearing for about 4 weeks. Management of postoperative pain allows for early mobilization, which contributes to faster resolution of swelling, promotes defect healing and joint nutrition, and prevents the development of adhesions. On the second postoperative day, self-assisted mobilization of the knee or continued passive motion 6 hours daily with 1 cycle per minute was recommended until 90° of flexion was attained. Controlled mobilization exercises with reduced range of motion, early isometric and isotonic exercises, and controlled mechanical compression were performed. In the third or fourth week, weight touchdown with crutches was allowed and was usually completed within 6 to 8 weeks after surgery. Most of the patients achieved full weightbearing by 6 weeks. Gait training in a swimming pool facilitated the recovery of normal gait phases.

At the beginning of the ninth week, active functional training was started. Symptoms of overloading (pain, effusion, tenderness) noticed by the surgeon or physical therapist were signals to retard the rehabilitation protocol. At 11 to 32 weeks after surgery, the rehabilitation goal was to return to a correct running pathway by proprioceptive, strength, and endurance exercises and aerobic training. When rehabilitation progresses without complication, this stage may end within 30 to 32 weeks after surgery. At the end of this time, the patient should be able to go up and down stairs and run forward at midspeed without symptoms. The remainder of rehabilitation was dedicated to the return to previous sport activity. Return to sports was allowed no earlier than 10 to 12 months after surgery.

Follow-up Evaluation

All 80 patients were evaluated preoperatively and at 2- and 5-year follow-up.

The clinical outcome of all patients was analyzed using the cartilage standard evaluation form as proposed by the International Cartilage Repair Society.[13] A knee function test was performed by the surgeon (not an independent reviewer) according to the International Knee Documentation Committee (IKDC) Knee Examination Form. The lowest ratings in effusion, passive motion deficit, and ligament examination were used to determine the final functional grade of the knee (normal, nearly normal, abnormal, or severely abnormal). A return to sporting activities was also recorded at 2- and 5-year follow-up, evaluated with the Tegner score,[32] and compared with preoperative and preinjury levels.

The operation was considered a failure if the patient needed a reoperation because of symptoms due to primary defects. For failed patients, the last clinical evaluation before reoperation was considered.

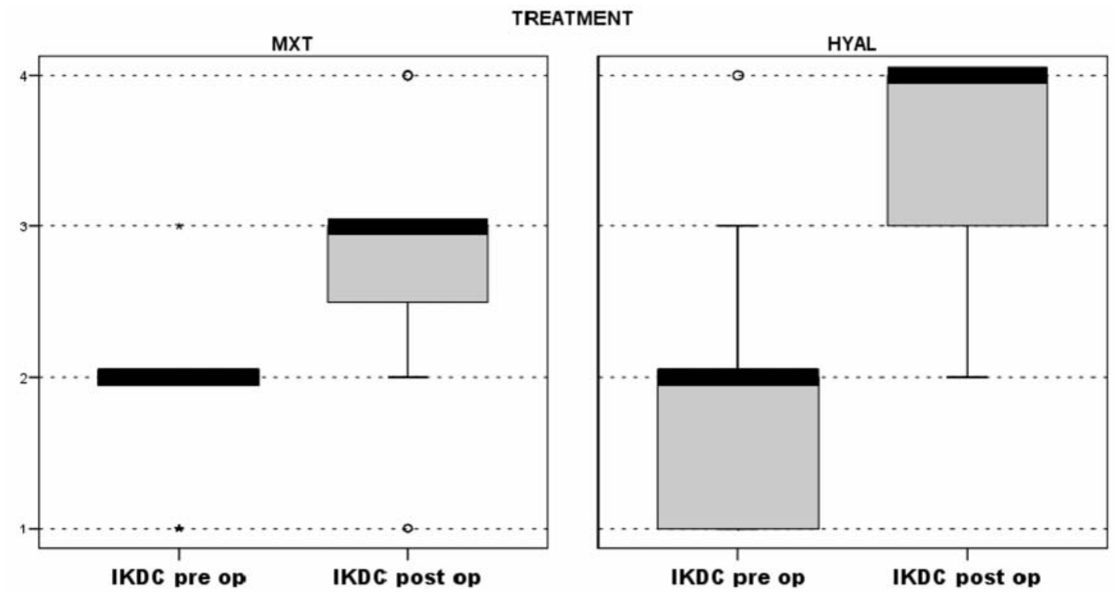

Figure 3. Comparison of the International Knee Documentation Committee (IKDC) objective scores achieved at 5-year follow-up by both groups of patients. The values are expressed in median and 25th and 75th percentiles. The microfracture (MXT) group improved from 2 (2-2) to 3 (2.5-3), and the Hyalograft C (HYAL) group improved from 2 (1-2) to 4 (3-4). Post op, postoperatively; pre op, preoperatively; 4, A (normal knee); 3, B (nearly normal); 2, C (abnormal); 1, D (severely abnormal).

Statistical Methods

All continuous variables were expressed in terms of mean ± standard deviation of the mean. The IKDC objective scores are expressed in terms of median and 25th and 75th percentiles. If the Kolmogorov-Smirnov test showed most continuous variables were not normal, a nonparametric test was performed. The Wilcoxon test was performed to test the hypotheses about continuous data differences between preinjury, preoperative, and follow-up evaluations. The Mann-Whitney test and Kruskal-Wallis test were used to test the hypotheses about continuous data differences between 2 treatments and among 3 different lesion size groups, respectively. The Pearson's χ^2 test was performed to investigate the difference in frequency distribution between 2 treatments. The Spearman rank correlation analysis was performed to investigate relationships between 2 continuous variables. The τ-b Kendall correlation analysis was performed to investigate relationships between IKDC and continuous variables. For all tests, $P < .05$ was considered significant.

A sample-size estimation showed that 40 patients in each group would be required to demonstrate a difference with IKDC subjective score of the 2 groups of at least 0.5 standard deviation from the mean (according to Cohen's conventions for a medium effect size) with an α level of .05 and a β level of 80%.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 14.1 (SPSS Inc, Chicago, Illinois).

RESULTS

No serious adverse events or surgery-related complications were observed during the treatment and follow-up periods. One case failed and was reoperated in the microfracture group; no failures requiring reoperation were detected in Hyalograft C group. Both groups showed statistically significant improvement of all clinical scores from preoperative to 5-year follow-up.

Group of patients treated with microfracture technique. The IKDC objective score increased from 2.5% normal and nearly normal knees before the operation (1 B, 32 C, and 7 D) to 75% normal and nearly normal knees (6 A, 24 B, 7 C, and 3 D) at 5-year follow-up and showed a statistically significant improvement (Wilcoxon test, $P < .001$) (Figure 3). There was a significant improvement in the IKDC subjective score from preoperative (41.1 ± 12.3) to 5-year follow-up (70.2 ± 14.7; Wilcoxon test, $P < .001$) (Figure 4). The sport activity, which was evaluated using the Tegner score, showed a statistically significant improvement (Wilcoxon test, $P < .001$) from preoperative level to 2- and 5-year follow-up; however, a decrease in sport activity from 2- to 5-year follow-up was documented (Wilcoxon test, $P < .001$) (Figure 5). One case that failed at the early stage (around 18 months of follow-up) was treated with autologous chondrocyte transplantation.

Group of patients treated with Hyalograft C. A statistically significant improvement in the IKDC objective score was observed (Wilcoxon test, $P < .001$), showing 15% normal or nearly normal knees preoperatively and 90% at

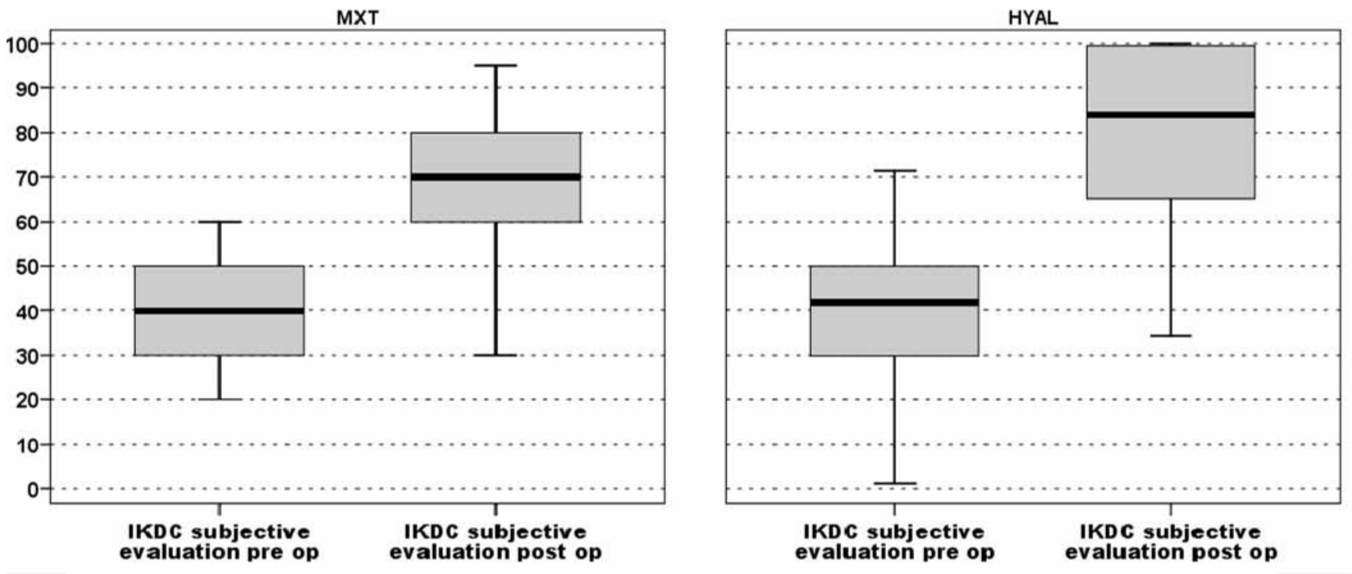

Figure 4. Comparison of the International Knee Documentation Committee (IKDC) subjective score achieved at 5-year follow-up by both groups of patients. The values are expressed in median and 25th and 75th percentiles. The microfracture (MXT) group improved from 40 (30-50) to 70 (60-80), and the Hyalograft C (HYAL) group improved from 42 (29-50) to 84 (63.5-99.5). Post op, postoperatively; pre op, preoperatively.

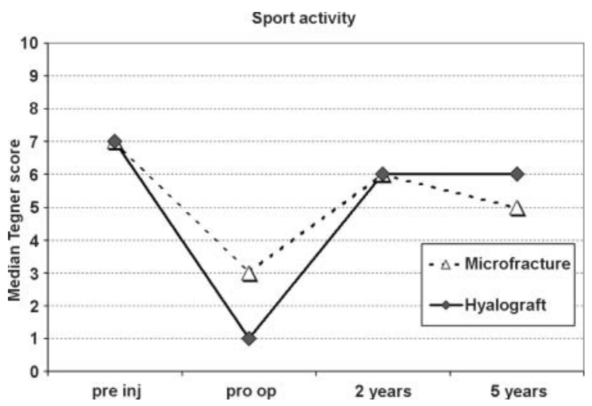

Figure 5. Trend of values of Tegner score in both groups of patients. In the microfracture group, scores passed from 7 (6-8) preinjury to 3 (3-4) preoperatively and improved to 6 (6-7) at 2-year follow-up and to 5 (4-6) at 5-year follow-up, whereas the Hyalograft C group passed from 7 (6-7) preinjury to 1 (1-3) preoperatively, with an improvement to 6 (3-7) at 2 years maintained at 5-year follow-up.

5-year follow-up (1 A, 4 B, 15 C, and 19 D preoperatively and 29 A, 6 B, and 5 C at 5-year follow-up) (Figure 3). There was a significant improvement for IKDC subjective score from preoperative (40.5 ± 15.2) to 5-year follow-up (80.2 ± 19.1; Wilcoxon test, $P < .001$) (Figure 4). The sport activity, evaluated with the Tegner score, showed a statistically significant improvement (Wilcoxon test, $P < .001$) from preoperative level to 2- and 5-year follow-up. The level of sport activity was maintained from 2-year follow-up to 5-year follow-up (Wilcoxon test, $P = .5$) (Figure 5).

When comparing the 2 groups, a higher improvement in the IKDC objective (Mann-Whitney, $P < .001$) and subjective (Mann-Whitney, $P = .003$) scores was observed in the group treated with Hyalograft C at 5-year follow-up (Figures 3 and 4). Analyzing the resumption of sports activity obtained with the Tegner score, we observed a return to sports at similar levels in both groups at 2-year follow-up, which remained stable at the 5-year follow-up in the Hyalograft C group, whereas it worsened in the microfracture group (Figure 5). In the group of patients treated with microfracture, 20 patients achieved the preinjury activity level at 2 years after surgery, but only 7 of the patients remained at the same level after 5 years. In the group of patients treated with Hyalograft C, 18 patients achieved the preinjury activity level at 2 years after surgery, and 18 of the patients were practicing sports at the same level after 5 years. In both groups, patient age was significantly correlated to sport activity resumption: older patients experienced greater difficulty in attempting to return to preinjury sport activity levels (Spearman rank correlation, $P = .05$). However, patient age has not influenced the clinical outcome evaluated with IKDC objective and subjective scores.

Other parameters such as size (Table 2) and mechanism of cartilage lesions and associated and previous surgery did not influence significantly the clinical outcome in both groups. A separate analysis of clinical outcome of the patients with associated ACL reconstruction was performed. No statistically significant differences were observed at 5-year follow-up in both treatment groups (Table 3).

TABLE 2
Analysis of the Clinical Outcome Related to the Defect Size[a]

		International Knee Documentation Committee		
Size of Lesion, cm^2	No. of Patients	Objective: 5-Year Median (25th-75th)	Subjective: 5-Year Mean (SD)	Tegner: 5-Year Median (25th-75th)
Overall				
<2	24	3.5 (3-4)	74.4 (15.8)	5.5 (4-6)
≥ 2 < 3	36	4 (3-4)	76.9 (19.5)	6 (4-7)
≥3	20	3 (3-4)	73.2 (17.0)	5 (3-5.5)
Kruskal-Wallis test		NS	NS	NS
Microfractures				
<2	11	3 (3-3)	73.6 (11.2)	5 (5-6)
≥2 <3	18	3 (2-3)	68.9 (17.3)	5 (4-6)
≥3	11	3 (2,5-3)	69.1 (13.9)	5 (3.5-5.5)
Kruskal Wallis test		NS	NS	NS
Hyalograft C				
<2	13	4 (4-4)	75.0 (19.3)	6 (4-6)
≥ 2 < 3	18	4 (4-4)	84.9 (18.6)	6.5 (3-7)
≥3	9	4 (3-4)	78.3 (19.9)	4 (3-5)
Kruskal-Wallis test		NS	NS	NS

[a]No statistically significant difference was found between groups. SD, standard deviation; NS, not significant.

TABLE 3
Separate Analysis of the Clinical Outcome of the Patients Who Underwent ACL Reconstruction[a]

		International Knee Documentation Committee		
Associated ACL Reconstruction	No. of Patients	Objective: 5-Year Median (25th-75th)	Subjective: 5-Year Mean (SD)	Tegner: 5-Year Mean (SD)
Overall				
Yes	36	3 (3-4)	75.7 (16.3)	5.7 (2.2)
No	44	3 (3-4)	74.9 (18.9)	4.8 (2.0)
Mann-Whitney test		NS	NS	NS
Microfractures				
Yes	20	3 (3-3)	70.8 (11.6)	5.6 (1.9)
No	20	3 (2-3)	69.8 (17.6)	5.0 (1.7)
Mann-Whitney test		NS	NS	NS
Hyalograft C				
Yes	16	4 (4-4)	81.8 (19.3)	5.8 (2.6)
No	24	4 (4-4)	79.1 (11.6)	4.7 (2.1)
Mann-Whitney test		NS	NS	NS

[a]No statistically significant difference was found between groups. SD, standard deviation; NS, not significant.

DISCUSSION

Several different surgical procedures have been proposed to treat cartilage injuries, but their indications and results are still controversial. Marrow stimulation procedures, such as drilling, abrasion, and microfracture, have been proposed as an easy, rapid, and inexpensive way to restore the articular damaged surface. Steadman et al[29] reported highly satisfactory results at 11-year follow-up with the microfracture technique, but patients had to adjust their activity levels to that of their knee function. However, the repair tissue response can be variable and unpredictable.[12,27] Most animal,[6,27] magnetic resonance imaging, and histological studies[21,23] have shown the initial fibrocartilage formation with deterioration of the newly formed tissue over time. Nehrer et al[23] frequently observed soft, spongiform, fibrous tissue combined with central degeneration in the defect. The clinical failure was observed at a mean follow-up of 21 months. Some authors have reported a significant decrease in clinical outcome at longer follow-up relative to short-term high satisfaction, especially in the athletic population.[8,15,16]

Autologous chondrocyte implantation proposed by Brittberg et al[3] in 1994 involves the reimplantation of autologous cells isolated from cartilage harvested from the patient and expanded in vitro. Peterson et al[24] and others[20,26] have shown that the early results obtained with the ACI technique are long lasting. The ACI presents some advantages over other cartilage repair and reconstructive techniques, including the use of autologous engineered material, reduced donor site morbidity, and no treatment limitations related to defect size. The most important theoretical advantage of this method is that it can restore the integrity of the damaged area with cartilage that has hyaline-like properties,[24] whereas all the marrow-stimulation techniques provide fibrocartilaginous repair tissue that is likely to be less mechanically stable. However, good results have to be weighed against the number of problems that can be observed with standard ACI methods. These include the difficulty in handling a delicate liquid suspension of chondrocytes at implantation surgery, the need to make a hermetic periosteum seal using sutures, the requirement of a second open surgery operation, the very long rehabilitation period, and possible complications associated with the use of a periosteal flap and large joint exposure. Moreover, the cell-based regenerative approach has not been clearly proved to be better than the marrow-stimulation techniques. A study of Knutsen et al[14] compared the microfracture technique with ACI and showed comparable clinical results in both groups at 5 years. Most published randomized trials compare the first-generation classic ACI, open surgery, and other arthroscopic techniques. The only randomized study that used second-generation ACI compared with chondroabrasion technique, presented by Visna et al,[33] reported significantly better results in the ACI group.

In this study, we compared microfracture with arthroscopic second-generation ACI on 3-dimensional scaffold that has shown comparable results to the traditional ACI technique but reduces the morbidity of the procedure.[7,18,19,22] Both techniques used in our study have demonstrated significant improvement in clinical outcomes at the 5-year follow-up. However, better clinical results assessed with objective and subjective IKDC scores at medium-term follow-up were found in the group treated with arthroscopic autologous chondrocyte transplantation. Also, no decrease in the resumption of sports activity from 2 to 5 years was observed in patients treated with autologous chondrocyte transplantation, whereas a decrease in sports activity was detected in the group treated with microfracture from 2- to 5-year follow-up. The reoperation rate was very low in our study in both groups; only 1 patient (in the microfracture group) was reoperated for clinical failure. Both groups were comparable for patient age, size and type of cartilaginous lesion, presence of associated surgery, and sport activity level. No different inclusion criteria were applied to decide the indication for 1 of 2 treatments. There were more patients who underwent previous surgery and fewer traumatic cartilage lesions in the Hyalograft C group relative to the microfracture group. This factor could potentially "penalize" the Hyalograft C group, considering that most clinical studies reported worse results in patients with degenerative lesions and in patients who underwent previous surgery, especially patients with previously failed cartilage surgery. But in our study, the patients treated with Hyalograft C showed improved results at 5-year follow-up. The main weakness in our study is represented by the fact that the 2 groups of patients were not randomized. However, the treatment was not determined by the surgeon's choice but by the policy of the institutions involved. In fact, it can be considered like a sort of "geographical selection." In this study, we analyzed a rather high number of patients at relatively long (5-year) follow-up. Most of the controlled clinical studies in the literature have a 2 year or shorter follow-up period. Moreover, most of the studies reported the results of second-generation matrix-induced autologous chondrocyte transplantation on less than 5-year follow-up.[17,22,31] Autologous chondrocyte transplantation on a 3-dimensional matrix was introduced in clinical practice in 1999, so it is very difficult to obtain medium- or long-term clinical findings. We found only 1 published clinical study[2] that reported a 5-year clinical outcome in 11 patients treated with matrix-associated autologous chondrocyte transplantation.

The high incidence of associated surgery also represents an important bias of our study. Unfortunately, the high presence of associated ACL and meniscal surgery is detectable in all cartilage clinical studies where traumatic cartilage lesions are treated. We tried to analyze statistically the influence of associated surgery and found no statistically significant difference between the patients with isolated chondral lesions and the patients who underwent associated surgery in both groups.

Most of the patients in our study were active and young, and all cartilaginous lesions were contained. Consequently, our results cannot be applied to older patients with large, uncontained degenerative lesions. The main disadvantage of autologous chondrocyte transplantation remains the high cost and 2-stage surgical procedure. However, our results have shown more durable good clinical results and sport activity resumption in the group treated with second-generation autologous chondrocyte transplantation. Long-term and randomized controlled studies will be needed to confirm these findings.

CONCLUSION

The analysis of 2 groups of patients treated with second-generation autologous chondrocyte transplantation on hyaluronan-based matrix and microfractures have shown satisfactory clinical outcomes at medium-term follow-up. We believe that second-generation autologous chondrocyte transplantation is a good and potentially durable option for the treatment of cartilage defects.

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REFERENCES

1. Aigner J, Tegeler J, Hutzler P, et al. Cartilage tissue engineering with novel nonwoven structured biomaterial based on hyaluronic acid benzyl ester. *J Biomed Mater Res*. 1998;42:172-181.
2. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (mact/maci): 5-year follow-up. *Knee*. 2006;13:194-202.
3. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331:889-895.
4. Brittberg M, Peterson L, Sjögren-Jansson E, Tallheden T, Lindahl A. Articular cartilage engineering with autologous chondrocyte transplantation: a review of recent developments. *J Bone Joint Surg Am*. 2003;85(suppl 3):109-115.
5. Brun P, Abatangelo G, Radice M, et al. Chondrocyte aggregation and reorganization into three-dimensional scaffolds. *J Biomed Mater Res*. 1999;46:337-346.
6. Dorotka R, Windberger U, Macfelda K, Bindreiter U, Toma C, Nehrer S. Repair of articular cartilage defects treated by microfracture and a three-dimensional collagen matrix. *Biomaterials*. 2005;26:3617-3629.
7. Gobbi A, Kon E, Berruto M, Francisco R, Filardo G, Marcacci M. Patellofemoral full-thickness chondral defects treated with hyalograft-c: a clinical, arthroscopic, and histologic review. *Am J Sports Med*. 2006;34:1763-1773.
8. Gobbi A, Nunag P, Malinowski K. Treatment of full thickness chondral lesions of the knee with microfracture in a group of athletes. *Knee Surg Sports Traumatol Arthrosc*. 2005;13:213-221.
9. Grigolo B, Lisignoli G, Piacentini A, et al. Evidence for redifferentiation of human chondrocytes grown on a hyaluronan-based biomaterial (hyaff 11): molecular, immunohistochemical and ultrastructural analysis. *Biomaterials*. 2002;23:1187-1195.
10. Grigolo B, Roseti L, Fiorini M, et al. Transplantation of chondrocytes seeded on a hyaluronan derivative (hyaff-11) into cartilage defects in rabbits. *Biomaterials*. 2001;22:2417-2424.
11. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint: a prospective, comparative trial. *J Bone Joint Surg Am*. 2003;85:185-192.
12. Hunziker EB. Articular cartilage repair: basic science and clinical progress: a review of the current status and prospects. *Osteoarthritis Cartilage*. 2002;10:432-463.
13. International Cartilage Repair Society. The cartilage standard evaluation form/knee. *ICRS Newsletter*. 1998;1:5-7.
14. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture: findings at five years. *J Bone Joint Surg Am*. 2007;89:2105-2112.
15. Kreuz PC, Erggelet C, Steinwachs MR, et al. Is microfracture of chondral defects in the knee associated with different results in patients aged 40 years or younger? *Arthroscopy*. 2006;22: 1180-1186.
16. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage*. 2006;14:1119-1125.
17. Marcacci M, Berruto M, Brocchetta D, et al. Articular cartilage engineering with hyalograft c: 3-year clinical results. *Clin Orthop Relat Res*. 2005;435:96-105.
18. Marcacci M, Kon E, Zaffagnini S, et al. Arthroscopic second generation autologous chondrocyte implantation. *Knee Surg Sports Traumatol Arthrosc*. 2007;15:610-619.
19. Marcacci M, Zaffagnini S, Kon E, Visani A, Iacono F, Loreti I. Arthroscopic autologous chondrocyte transplantation: technical note. *Knee Surg Sports Traumatol Arthrosc*. 2002;10:154-159.
20. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop Relat Res*. 2001;391:S349-S361.
21. Mithoefer K, Williams RJ III, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee: a prospective cohort study. *J Bone Joint Surg Am*. 2005;87:1911-1920.
22. Nehrer S, Domayer S, Dorotka R, Schatz K, Bindreiter U, Kotz R. Three-year clinical outcome after chondrocyte transplantation using a hyaluronan matrix for cartilage repair. *Eur J Radiol*. 2006;57:3-8.
23. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res*. 1999;365:149-162.
24. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation: biomechanics and long-term durability. *Am J Sports Med*. 2002;30:2-12.
25. Peterson L, Minas T, Brittberg M, Nilsson A, Sjögren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res*. 2000;374:212-234.
26. Sgaglione NA, Miniaci A, Gillogly SD, Carter TR. Update on advanced surgical techniques in the treatment of traumatic focal articular cartilage lesions in the knee. *Arthroscopy*. 2002;18:9-32.
27. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg Am*. 1993;75:532-553.
28. Solchaga LA, Dennis JE, Goldberg VM, Caplan AI. Hyaluronic acid-based polymers as cell carriers for tissue-engineered repair of bone and cartilage. *J Orthop Res*. 1999;17:205-213.
29. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy*. 2003;19:477-484.
30. Steadman JR, Rodkey WG, Briggs KK. Microfracture to treat full-thickness chondral defects: surgical technique, rehabilitation, and outcomes. *J Knee Surg*. 2002;15:170-176.
31. Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up. *Arthroscopy*. 2007;23:381-387.
32. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res*. 1985;198:43-49.
33. Visna P, Pasa L, Cizmár I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques: a randomized controlled study. *Acta Chir Belg*. 2004;104:709-714.