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Treatment of isolated chondral and osteochondral defects in the knee by autologous matrix-induced chondrogenesis (AMIC)

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Abstract
Purpose The purpose of this study is to evaluate clinical and radiological outcomes of patients treated with autologous matrix-induced chondrogenesis (AMIC) for full-thickness chondral and osteochondral defects of the femoral condyles and patella.
Method A retrospective evaluation of clinical and radiographic outcomes of patients treated with AMIC for chondral and osteochondral full-thickness cartilage defects of the knee was performed with a mean follow-up of 28.8 ± 1.5 months (range, 13–51 months).
Results Significant improvements in clinical outcome scores (IKDC, Lysholm, Tegner, and VAS pain score) were noted. The largest improvements were seen in the osteochondral subgroup (mean age 25.9 years), whereas patients treated for chondral defects in the patellofemoral joint and on the femoral condyles improved less. Patients in all groups were generally satisfied with their results. MRI evaluation showed that tissue filling was present but generally not complete or homogenous.
Conclusions AMIC is a safe procedure and leads to clinical improvement of symptomatic full-thickness chondral and osteochondral defects and to regenerative defect filling. The value of AMIC relative to other cartilage repair procedures and to the natural course remains undefined.
Level of evidence Case series, Level IV.

Keywords Autologous matrix-induced chondrogenesis (AMIC) · Chondrocyte · Chondral defect · Osteochondral defect · Bone marrow stimulation

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Introduction

There are numerous causes of isolated chondral and osteochondral defects, but the majority are due to either trauma or osteochonditis dissecans. Damaged articular cartilage has limited or no healing capacity [6, 31]. These lesions occur most frequently in the knee; can cause significant pain, locking, and swelling; and can lead to osteoarthritis [14]. Repairing isolated full-thickness chondral and osteochondral defects has therefore been proposed to improve symptoms and potentially avoid progression to osteoarthritis.

In 1959, Pridie was the first to introduce the concept of drilling the subchondral bone to form a fibrocartilaginous surface [30]. Steadman improved upon this concept by introducing the microfracture technique, which avoids heat necrosis caused by the drill [37, 38]. Bleeding from the holes in the subchondral bone leads to the formation of a blood clot containing mesenchymal stem cells and growth factors arising from the bone marrow. Within a

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few weeks, the blood clot is replaced by vascularized, scar-like fibrocartilage and potentially hyalin-like tissue [16, 23, 35].

A potential limitation of all such marrow stimulation techniques is that the bone marrow stem cells are simply released into the joint rather than being contained at the site of the cartilage defect. To address this limitation, Behrens developed the technique of autologous matrix-induced chondrogenesis (AMIC) [1]. By covering the defect with a collagen matrix following microfracture, the surgeon produces a "bio-reactor" in which mesenchymal stem cells and growth factors released from the bone marrow are entrapped and concentrated, potentially improving their ability to restore cartilage in the defect.

Results of the AMIC technique have only been reported by the author who first described the technique, or with several modifications [2, 3, 8, 9, 11, 27, 29, 34, 41]. Although the AMIC technique is becoming established as a treatment option, no independent clinical results of the unmodified technique are available. The purpose of this study was to evaluate clinical and radiological outcomes of patients treated with AMIC for osteochondral and full-thickness chondral defects of the knee. The hypothesis was that AMIC leads to clinical improvement of cartilage defects and relieves symptoms.

Materials and methods

Following institutional review board approval, a retrospective review of all patients with osteochondral and full-thickness chondral defects treated with AMIC between August 2003 and July 2006 was done. Patients treated for defects in locations other than the knee were excluded.

Surgical indications

AMIC was only performed in patients meeting specific criteria. All had isolated chondral or osteochondral lesions on weight-bearing portions of the femoral condyles or the patellofemoral joint. Both traumatic and atraumatic lesions were included. All chondral lesions were grade III or IV [5], at least 2 cm^2 in area, and were surrounded with intact cartilage. Patients were all skeletally mature but under age 50. Patients were included regardless of limb alignment. In cases of a medial or lateral femoral condyle damage associated with more than 2° of mechanical varus or valgus axis, a realignment osteotomy was performed in conjunction with the AMIC procedure. In cases of patella maltracking in association with a patellofemoral cartilage lesion, a tibial tubercle realignment procedure was done.

Surgical technique

All cases were performed by the senior author (RPJ) or under his supervision. Under regional or general anesthesia and antibiotic prophylaxis, a tourniquet was applied to the thigh. The status of the cartilage lesion was assessed by arthroscopy, including location, size, and depth according to the ICRS classification [5]. A concurrent osteotomy was performed in cases of varus and valgus malalignment or patellar maltracking with a cartilage lesion of the associated compartment. In cases with varus axis, medial open-wedge high tibial osteotomy was done, whereas for valgus axis, supracondylar medial closing wedge osteotomy was performed [26, 36]. Patellar maltracking was approached with medialization of the tibial tuberosity in combination with lateral release [7, 22].

AMIC technique (Fig. 1): Following assessment of the defect and correction of any malalignment, an arthrotomy was performed and the cartilage lesion was debrided. Loose chondral flaps and necrotic tissue were removed and a clear border of normal adjacent cartilage defined. The calcified chondral layer was removed with a burr, and microfracture was performed according to the technique described by Steadman [38]. The holes were created with 3–4-mm space between them, resulting in about four perforations per cm^2. By use of an imprint of the cartilage defect, a collagen matrix (Chondro-Gide®, Geistlich, Wolhusen, Switzerland) was cut to fit the defect shape.

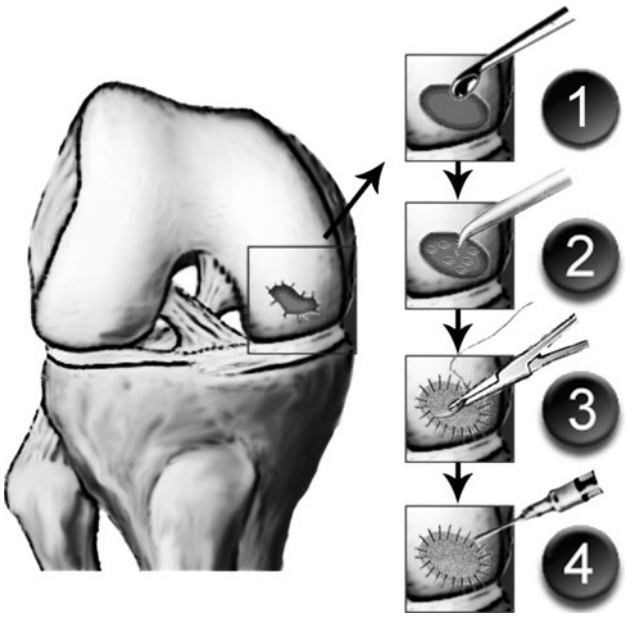

Fig. 1 The AMIC procedure. (*1*) Debridement of injured cartilage; (*2*) Microfracture is performed by penetrating the subchondral layer with 3–4-mm space between holes; (*3*) a collagen matrix is sutured to the defect; and (*4*) fibrin glue is injected under the matrix to improve fixation

It was sutured into the defect with the rough side facing the subchondral bone plate using 5–0 polydioxanone suture. Special attention was paid to obtaining a smooth transition between the matrix and healthy cartilage. Partial autologous fibrin glue (Tissucol, Baxter, Vienna, Austria) was prepared using a method in which half the thrombin was discarded and replaced by the patient's serum mixed with a syringe. This fibrin glue was injected under the matrix to improve fixation. The stability of the matrix was assessed by extending and flexing the knee.

In cases of an osteochondral defect, involved bony tissue was removed and the resulting defect was filled with autologous cancellous bone from the iliac crest or tibial metaphysis mixed with hydroxyapatite (Orthoss®, Geistlich, Wolhusen, Switzerland) [19]. The matrix was sutured to the surrounding cartilage, and partial fibrin glue was added as described above.

Rehabilitation

Starting on the first post-operative day, patients were instructed to use crutches to maintain partial weight-bearing of 15–20 kg for 6 weeks. A removable brace locked in extension was utilized during ambulation. Passive range of motion began on day 10 using a continuous passive motion machine from 0 to 60° for 4 weeks and then increased to from 0 to 90°. Unrestricted weight-bearing and range of motion were encouraged after 6 weeks. If an osteotomy was included in the procedure, full weight-bearing was delayed until bony consolidation was noted, generally around 6 weeks but longer in some cases. Patients participated in physical therapy to improve strength and range of motion. Permission to participate in unrestricted sports activity was given after 12 months.

Outcome measures

Demographic data (age, sex, and body mass index), affected side, lesion location and size, interval between onset of symptoms and surgery, concurrent procedures, and number of previous surgeries were obtained from the medical record. Clinical evaluation was undertaken by a clinical fellow within our department before and after surgery with a minimum follow-up of 12 months. Four scoring systems were used: (1) International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form [13, 18]; (2) modified Lysholm Knee Scoring Scale [39]; (3) Tegner Activity Score [39] and (4) a Visual Analog pain Scale (VAS) [17]. Patients also indicated their satisfaction with the surgery on a scale from 0% (completely dissatisfied) to 100% (completely satisfied).

Radiological evaluation was based on MRI examination at a minimum follow-up of 12 months. MRI was not performed in patients with metallic hardware in place from osteomies because artifact was anticipated to prevent accurate analysis. A standard protocol for knee MRI with proton density and fast spin-echo acquisitions for cartilage evaluation was performed using a circular, polarized knee coil (coil diameter 17 cm). For specific high-resolution imaging, a surface phased array coil (coil diameter, 8 cm) was placed over the knee compartment of interest (site of cartilage repair). This protocol has been described by Marlovits et al. [24, 25] who defined suitable assessment of cartilage repair tissue by the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) classification and grading system. An experienced radiologist with expertise in assessment of musculoskeletal disorders who was blinded to the clinical outcome assessed the MRI data according to the MOCART system.

Statistical analyses

Descriptive statistics for all data included the arithmetic mean and standard deviation. Based on the data characteristics, significance was calculated with Wilcoxon signed-rank test, Kruskal–Wallis one-way analysis of variance and Chi-square test. A P value of less than 0.05 was considered significant. Statistical analyses were carried out using SPSS Version 17.0.1 (SPSS Incorporated, Chicago, IL, USA).

Results

Thirty-eight patients including two bilateral cases (40 knees) were treated with AMIC during the study period with a mean follow-up of 28.8 ± 1.5 months (range, 13–51 months). No patients were lost to follow-up. Based on defect location and type, the study group was categorized as 20 full-thickness chondral defects of the patella (cP group), 9 full-thickness chondral defects of the femoral condyle (cF group), and 11 osteochondral defects of the femoral condyle due to osteochondritis dissecans (ocF group). Comparison of pre-operative data between the subgroups revealed no significant differences with the exceptions of smaller defect area in the cF groups and decreased patient age and lower incidence of associated osteotomy in the ocF group (Table 1).

Clinical outcome

Clinical outcome was evaluated using four scoring systems (IKDC, Lysholm, Tegner, VAS). Pre-operatively, no significant differences were noted in clinical scores between the subgroups (Table 2). The entire study group significantly improved in all four scores from the pre-operative

Table 1 Pre-operative characteristics of the study subgroup

	ocF group	cP group	cF group	Significance
Knees (*n*)	11	20	9	
Age (years ± SD)	**25.9 ± 3.1**	39.2 ± 2.8	39.4 ± 3.6	***P* = 0.0156**
Sex	5 male	10 male	8 male	n.s.
	6 female	10 female	1 female	
Side	5 left	9 left	3 left	n.s.
	6 right	11 right	6 right	
MFC/LFC	11 MFC	NA	5 MFC	n.s.
	0 LFC		4 LFC	
Body mass index (kg/m^2 ± SD)	26.3 ± 1.9	25.2 ± 0.9	25.7 ± 0.9	n.s.
Number of previous surgeries (*n* ± SD)	1.0 ± 0.5	1.1 ± 0.3	1.2 ± 0.3	n.s.
Interval symptoms to surgery (months ± SD)	56.9 ± 26.8	112.3 ± 24.1	54.5 ± 19.5	n.s.
Area (cm^2 ± SD)	4.2 ± 0.4	4.4 ± 0.6	**2.3 ± 0.4**	***P* = 0.0227**
Follow-up (months ± SD)	27 ± 2.3	29.3 ± 2.3	29.6 ± 3.2	n.s.
Associated osteotomy performed	4/11 (36%)	18/20 (90%)	6/9 (67%)	***P* = 0.0075**

ocF osteochondral femoral condyle group, *cP* chondral patella group, *cF* chondral femoral condyle group, *MFC* medial femoral condyle, *LFC* lateral femoral condyle, *SD* standard deviation

Bold indicates a statistically significant difference

Table 2 Clinical outcome scores assessment

	ocF ($n = 11$)	cP ($n = 20$)	cF ($n = 9$)	Significant difference among groups
IKDC pre-surgery	44 ± 25	51 ± 25	45 ± 26	n.s.
IKDC follow-up	88 ± 9	74 ± 17	68 ± 14	***P* = 0.0016**
Significance pre- versus post-operative	***P* = 0.005**	***P* = 0.0025**	n.s.	
Lysholm pre-surgery	50 ± 25	58 ± 17	56 ± 25	n.s.
Lysholm follow-up	94 ± 8	85 ± 13	76 ± 18	***P* = 0.0158**
Significance pre- versus post-operative	***P* = 0.0051**	***P* < 0.0001**	n.s.	
Tegner pre-surgery	2 ± 2	3 ± 2	4 ± 3	n.s.
Tegner follow-up	5 ± 2	4 ± 1	4 ± 1	n.s.
Significance pre- versus post-operative	***P* = 0.0115**	n.s.	n.s.	
VAS pre-surgery	6 ± 3	6 ± 2	6 ± 3	n.s.
VAS follow-up	1 ± 1	2 ± 2	3 ± 3	***P* = 0.0151**
Significance pre- versus post-operative	***P* = 0.0048**	***P* = 0.0004**	n.s.	
Satisfaction index [%]	98 ± 4	84 ± 24	74 ± 43	n.s.

ocF osteochondral femoral condyle group, *cP* chondral patella group, *cF* chondral femoral condyle group, *IKDC* International Knee Documentation Committee score; *VAS* visual analog scale

Bold indicates a statistically significant difference

evaluation to follow-up (IKDC, Lysholm and VAS: $P < 0.0001$; Tegner: $P = 0.006$). However, the improvements in the cF group were not significant, whereas the ocF and cP groups improved significantly (Table 2). Patients treated with AMIC alone were compared with patients who had an associated unloading procedure. No significant differences in outcome were noted based on whether an associated osteotomy was performed. Patient satisfaction evaluated using the satisfaction index was high in all groups (Table 2).

Radiological outcome

Twenty-four of the 40 knees (60%) had no metallic hardware in place and underwent MRI evaluation. However, signal artifact precluded analysis of the cartilage tissue of interest in eight patients (seven in the cP group), likely due to metal debris left by the dental burr. The remaining 16 patients were evaluated according to the MOCART system (Table 3). Results were inconsistent, with some patients demonstrating good defect filling while others demonstrated no filling or hypertrophy. Integration to the border zone was generally good, but abnormalities of subchondral bone and lamina were common. Nearly all patients demonstrated increased signal in the repair tissue.

Complications

In the early post-operative period, one patient developed a hematoma that underwent evacuation. Nine patients (all in the cP group) needed mobilization under anesthesia due to

Table 3 MOCART evaluation of all patients at follow-up

Variable	Description	Cases
1 Degree of defect repair and filling of the defect	Complete	3
	Hypertrophy	3
	Incomplete >50% of the adjacent cartilage	4
	Incomplete <50% of the adjacent cartilage	4
	Subchondral bone exposed	2
2 Integration to border zone	Complete	8
	Demarcating border visible (split-like)	4
	Defect visible <50% of the length of the repair tissue	3
	Defect visible >50% of the length of the repair tissue	1
3 Surface of repair tissue	Surface intact	2
	Surface damaged <50% of repair tissue depth	8
	Surface damaged >50% of repair tissue depth	6
4 Structure of repair tissue	Homogenous	0
	Inhomogenous or cleft formation	16
5a Signal intensity of repair tissue Dual T2-FSE	Isointense	1
	Moderately hyperintense	0
	Markedly hyperintense	15
5b 3D-GE-FS	Isointense	0
	Moderately hyperintense	0
	Markedly hyperintense	16
6 Subchondral Lamina	Intact	3
	Not intact	13
7 Subchondral bone	Intact	4
	Non-intact	12
8 Adhesions	No	15
	Yes	1
9 Effusion	No	6
	Yes	10

knee stiffness. All regained full range of motion following mobilization.

Discussion

The most important findings of the present study were that both AMIC alone and AMIC in combination with unloading osteotomy or patella realignment significantly improved symptomatic knees with isolated osteochondral and chondral lesions in the knee joint. However, less improvement was noted in the subgroup with purely chondral defects of the femoral condyle compared to the subgroup with chondral defects on the patella and the subgroup with osteochondral defects of the femoral condyles.

The reasons for the differing findings within the subgroups are not clear. The natural history of osteochondritis dissecans lesions may be better than that of isolated purely chondral defects, potentially improving the results following AMIC in this group as well. Further, the additional curettage and bone grafting performed in the osteochondral group may contribute to the recruitment of additional stem cells to the area. It is also likely that numerous factors not directly related to the defects themselves contributed to the poorer results in the femoral chondral lesion group. One major factor may have been the higher age of patients in this group. It has been shown in vitro that stem bone marrow cells from older patients have less chondrogenic potential than cells from younger patients, potentially decreasing the effectiveness of AMIC in older patient groups [28]. Conversely, the defect size in the cF group was significantly smaller than in the two other groups, which was expected to be favorable in regard to outcome. Another important observation was the high complication rate (knee stiffness) in the cP subgroup. All of them regained full range of motion after mobilization under anesthesia. After reviewing our findings, we have changed our post-operative rehabilitation protocol to include early knee mobilization to overcome this problem.

Three studies with clinical and MRI results of a comparable AMIC technique are available in the literature [11, 34, 41]. Comparing the present results to this study revealed similar improvements in outcome.

Unlike standard microfracture, autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), or mosaicplasty [4, 12, 15, 20, 21, 32, 33, 40], AMIC has not been evaluated with randomized controlled trials. Such trials and prospective cohort studies are necessary to determine appropriate indications for AMIC. However, until such studies are available, retrospective comparative works such as the current study can provide valuable insights into which populations benefit most from this treatment. Furthermore, this is the first case series of the unmodified AMIC technique that is independent of the author who originally described the technique.

Strengths of the study include 100% follow-up at a mean of 28 months following surgery, the use of numerous validated clinical outcome scores, and the use of MRI to assess the newly formed cartilage. MRI has been shown to provide good information on the quality of cartilage repair tissue [24, 25]. However, metal artifact precluded MRI evaluation in most cases of the cP subgroup. The MRI findings in this study are similar to those reported in prior AMIC series, with variable filling, good border zone

integration, and the persistence of abnormally increased MRI signal in the newly formed cartilage [10, 11].

Weaknesses of the study include its retrospective nature and the fact that the AMIC procedure was frequently not performed in isolation. An unloading osteotomy or realignment procedure was performed concurrently in the majority of cases to unload the area of abnormal cartilage. While it is unclear how much of the symptomatic improvement in each patient was provided by the osteotomy and how much was provided by AMIC, we noted no significant differences in the amount of improvement seen in patients who underwent a concurrent unloading and those who did not. Further, the relatively short follow-up in the current study does not allow assessment of the effectiveness of this procedure in the prevention of diffuse degenerative changes. In addition, it must be pointed out that several steps of the AMIC procedure are not scientifically validated, such as the role of the partial fibrin glue administration or the role of the collagen matrix. This study does not address this knowledge gap, and further investigation is therefore needed.

Conclusion

The AMIC procedure alone and in association with an unloading procedure significantly improved clinical outcome scores in patients with isolated chondral and osteochondral defects in the knee joint. Tissue filling was present but often not complete or homogenous when evaluated with MRI. The importance of an associated unloading procedure and the indications for AMIC compared to other cartilage repair techniques need to be validated in further studies.

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