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Good clinical results with autologous matrix-induced chondrogenesis (Amic) technique in large knee chondral defects

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Abstract
Purpose Autologous matrix-induced chondrogenesis (AMIC) is a treatment for focal full-thickness cartilage defects combining microfracturing with an exogenous I/III collagen matrix (Chondro-Gide). The aim of the present study was to determine the 7 years outcomes of patients treated with the AMIC technique for knee chondral defects larger than 2 cm^2. The hypothesis was that the positive short-term outcomes achieved in the previous series would not deteriorate at a 7-year follow-up.
Methods Twenty-one patients treated with the AMIC technique were retrospectively analysed. Patients were assessed through the IKDC subjective knee evaluation questionnaire and the Lysholm scoring system. All patients underwent a complete imaging study including radiographs and magnetic resonance. The median defect size was found to be 4.3 (range 2.9–8) cm^2.
Results At a median follow-up of 7 (±1.4) years, the mean IKDC score improved from 31.7 (±8.9) points preoperatively, to 80.6 (±5.3) at the latest follow-up ($p < 0.05$). The mean Lysholm score improved from 38.8 (±12.4) points preoperatively to 72.6 (±19.5) points at the last follow-up ($p < 0.05$). At the last follow-up, 76.2% of patients were satisfied or extremely satisfied with their outcomes, while 66.6% of patients showed good quality repair tissue on magnetic resonance imaging.
Conclusion AMIC was found to be an effective method to treat full-thickness knee chondral defects larger than 2 cm^2, with significant clinical and functional improvement maintained over a 7-year follow-up.
Level of evidence IV.

Keywords Knee chondral defects · AMIC · Chondrogenesis · Microfracturing · Chondro-Gide

Introduction

Focal knee cartilaginous defects affect a wide spectrum of patients [5–10]. In a study, Arøen et al. [2] found that the full-thickness cartilage defects suitable for repair procedures were found in 11% of 1000 knee arthroscopies, and of these, 55% (6% of all knees) had a size above 2 cm^2.

Repairing isolated full-thickness knee chondral defects is known to improve symptoms (pain, limited function, stiffness) and potentially prevent progression to osteoarthritis [16]. To be effective, a cartilage repair procedure should recreate hyaline-like cartilage [9]. Surgical treatment of knee chondral lesions has greatly evolved in the last 20 years, where several procedures have been used with variable success rates. Nowadays, the microfracturing technique remains the simplest method to recruit bone marrow mesenchymal stem cells (MSCs) to the site of a chondral defect. MSCs represent a potential source of cells for cartilaginous regeneration [15]; in fact, MSCs are able to differentiate into fibro-chondrocytes that contribute to fibrocartilage repair of the lesion [21]. Since the fibrin network of the blood clot deriving from the microfracturing and

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containing the MSCs maybe not stable enough to sustain the tangential forces of the knee [4], the consequent weakness of the final cartilaginous repair tissue may lead to its early breakdown under normal knee loading. The use of an exogenous scaffold (e.g. collagen matrix) can provide mechanical stability for the primary cartilaginous repair tissue and can additionally represent a proper stimulation for MSCs towards chondrogenic differentiation and cartilage regeneration [11]. Accordingly, AMIC technique provides a solution by combining microfracturing with a collagen I/III matrix (Chondro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) [6]. Chondro-Gide is a type I/III porcine collagen membrane with two layers: the superficial compact layer acts as a smooth barrier surface to prevent MSCs from spreading into the joint, while the deep porous layer promotes cell uptake and adhesion. The AMIC technique is recognized as a cost-effective, one-step procedure requiring neither cartilage harvesting nor in-vitro cell-expansion [8]. While the microfracturing technique is generally recommended for small chondral defects (<2 cm^2), the AMIC technique provides an effective solution for larger defects [1]. Anyway, concerns remain about the mid-term clinical results of the AMIC technique for large knee chondral defects.

The aim of the present study was therefore to determine the 7 years outcomes of patients treated with the AMIC technique for large knee chondral defects. The hypothesis was that the positive short-term outcomes achieved in the previous series [20] would not deteriorate at a 7-year follow-up.

Materials and methods

Twenty-one patients treated with AMIC technique for focal full-thickness knee chondral defects were retrospectively analysed. Indications for the AMIC procedure were symptomatic full-thickness ICRS grade 4 chondral lesions larger than 2 cm^2. The exclusion criteria were kissing lesions, chronic inflammatory synovitis, body mass index (BMI) higher than 35 kg/m^2, severe tibio-femoral and/or patello-femoral malalignment, ligament insufficiency and complete meniscal resection. Preoperatively, patients were assessed through the International Knee Documentation Committee (IKDC) subjective knee evaluation questionnaire and the Lysholm scoring system. All patients underwent a complete imaging study including weight-bearing long-leg anteroposterior view radiographs as well as Rosenberg, Merchant and lateral projections, and a MRI evaluation. Postoperatively, patients were clinically assessed at 3, 6, 12 months and then yearly through the IKDC questionnaire and the Lysholm scoring system. MRI was performed in 1 and 7 years after the surgery using a 1.5-T system. A single T2 slice 90° to the largest portion of the lesion was chosen for evaluation according to a modified magnetic resonance observation of cartilage repair tissue (MOCART) scoring system. The ethics committee of the University of Molise does not require its approval for the review of patient records or images.

The technique, previously described [19], was performed in a single-session surgery. Arthroscopy was first performed using standard portals to examine the knee joint and to confirm size, depth and location of the defect. A minimally invasive arthrotomy was then performed according to the location of the defect. Median defect size was found to be 4.3 (range 2.9–8) cm^2. The medial condyle was affected in 11 cases, lateral condyle in 3 cases, femoral trochlea in 6 cases and patella in 1 case. After removing the unstable cartilage surrounding the defect and debriding all calcified cartilage until healthy-looking bone appeared, an aluminium template was used to choose the correct size and shape of the definitive Chondro-Gide membrane. At this point, bone marrow mesenchymal stimulation was performed through microfracturing. In the first two patients of this case series, mesenchymal stimulation was achieved through a standard microfracturing technique. In the remaining 19 patients, mesenchymal stimulation was realized through free-hand drilling with a 1.1-K wire since this procedure has proven to recruit a higher number of MSCs than microfracturing [13]. The Chondro-Gide membrane was trimmed to fit the defect and fixed with fibrin glue (Fig. 1). The knee was gently moved at the end of the surgery to confirm that the membrane remained in place. No drainage was used.

When condyles were treated, immediate weight-bearing, active and passive (up to 90°) knee mobilization and isometric muscle strengthening exercises were started from the first postoperative day under the supervision of a physical therapist. At 30-day postoperative, increasing weight-bearing and flexion beyond 90° were allowed. When patello-femoral defects were treated, immediate weight-bearing was allowed although knee flexion was limited to 60° for the first 30 days. Then, progressive increase of the knee flexion was allowed. Heavy work activities or competitive sport activities were allowed postoperatively at 3 and 6 months, respectively.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 13 for Windows. Descriptive statistics (mean ± standard deviation; 95% confidence intervals) were used to profile IKDC and Lysholm scores at each time point of assessment (baseline, 36 months and 84 months). The normality assumption of the data was evaluated with the Shapiro–Wilk test ($p > 0.05$).

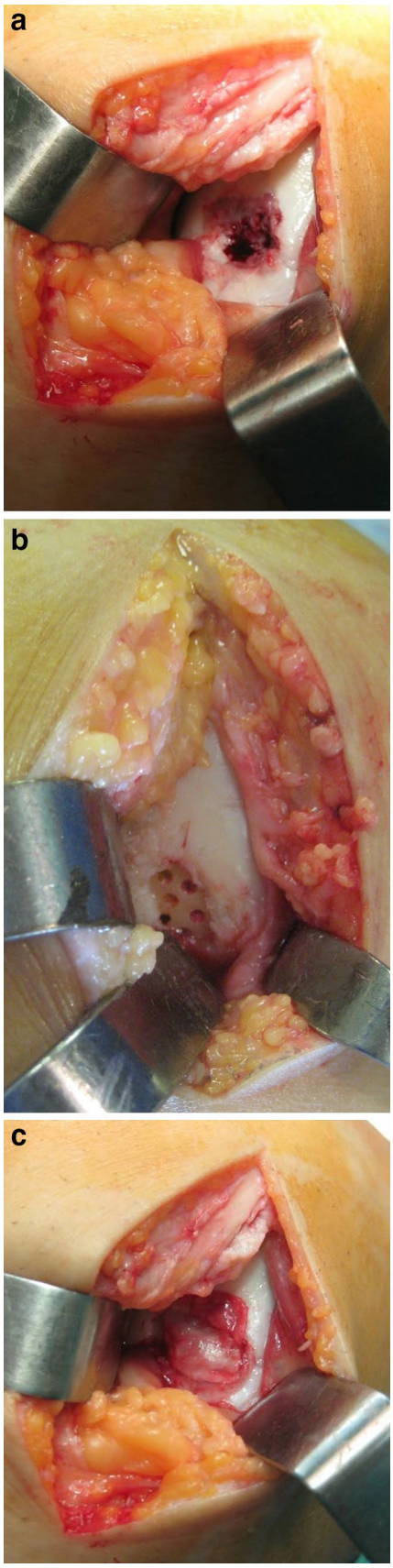

Fig. 1 Knee chondral defect of the mediale femoral condyle before (**a**) and after (**b**) microfracturing. Chondro-Gide membrane implanted (**c**)

According to this evaluation, the difference between before (T0) and after treatment (T1 and T2) were compared with repeated measures ANOVA. Additionally, Spearman correlation analyses were performed to analyse the correlation between functional scores at each time point of assessment baseline (T0), 36 months (T1) and 84 months (T2) of anatomical locations (Medial Condyle, Lateral Condyle and Patello-femoral) versus age and BMI of patients. The level of significance was set at $p < 0.05$.

Results

The median follow-up was 7 years (range 6.5–8 years). The mean IKDC score improved from 31.7 (±8.9) points preoperatively, to 80.6 (±5.3) at the latest follow-up ($p < 0.05$). The mean Lysholm score improved from 38.8 (±12.4) points preoperatively, to 72.6 (±19.5) points at the last follow-up ($p < 0.05$). The significant improvement of the clinical and functional results was maintained over time to the latest follow-up.

A repeated measures of ANOVA with a Greenhouse-Geisser correction determined that the mean of IKDC ($p < 0.0005$) and Lysholm ($p < 0.005$) scores differed statistically significantly between time points. Post-hoc tests using Bonferroni correction revealed significant improvement in functional scores after 3 years ($p < 0.0005$), which were sustained after 7 years ($p < 0.0005$).

No significant correlation was found between patient age and BMI versus functional scores ($p > 0.05$). At the latest follow-up, 16 (76.2%) of the patients were either satisfied or extremely satisfied with their clinical and functional outcomes. The MOCART score was applied for morphological evaluation of the repair tissue (Table 1). On MRI evaluation (Fig. 2), reduction both of the defect area and subchondral edema were present in 14 (66.6%) patients.

Discussion

The most important finding of this study was that AMIC was found to be effective in treating full-thickness knee chondral defects larger than 2 cm^2, with significant clinical and functional improvement at a median follow-up of 7 years. Additionally, these positive outcomes did not deteriorate over time but were maintained until the latest follow-up, therefore confirming the initial hypothesis.

The AMIC technique combines the advantages of the mesenchymal stimulation through microfracturing with

Table 1 Evaluation of cartilage repair tissue ($n=21$) at 7-year follow-up using MOCART score

Variables	Points for scoring	Number of patients at 1 year	Number of patients at 7 years
Degree of defect repair and filling of the defect			
Complete	20	15	14
Hypertrophy	15	0	0
Incomplete >50% of the adjacent cartilage	10	4	5
Incomplete >50% of the adjacent cartilage	5	2	2
Subchondral bone exposed	0	0	0
Integration of border zone			
Complete	15	14	14
Incomplete, demarcating border visible	10	4	4
Incomplete, defect visible <50% of the length	5	2	2
Incomplete, defect visible >50% of the length	0	1	1
Surface of the repair tissue			
Surface intact	10	15	14
Surface damaged <50% of depth	5	3	4
Surface damaged >50% of depth	0	3	3
Structure of the repair tissue			
Homogeneous	5	14	16
Inhomogeneous	0	7	5
Signal intensity of the repair tissue (Dual FSE)			
Isointense	15	3	5
Moderately hyperintense	5	15	14
Markedly hyperintense	0	3	2
Signal intensity of the repair tissue (3D gradient)			
Isointense	15	3	5
Moderately hypointense	5	15	14
Markedly hypointense	0	3	2
Subchondral lamina			
Intact	5	10	9
Not intact	0	11	12
Subchondral bone			
Intact	5	12	12
Not intact (edema, granulation tissue, cysts, sclerosis)	0	9	9
Adhesions			
No	5	21	21
Yes	0	0	0
Effusion			
No	5	19	20
Yes	0	2	1

the use of an exogenous scaffold acting as a framework for new cells. Gille et al. [12] have already shown significant improvements of clinical and functional scores in 27 patients with 32 knee chondral defects treated with the AMIC procedure. The median defect size of the chondral lesions was 4.2 (range 1.3–8.8) cm^2. Twenty out of 23 (87%) individuals were subjectively highly satisfied with the results after surgery. The postoperative MRI showed moderate to complete filling in most cases. However, the median follow-up was only 37 (range, 24 to 62) months. Similarly, Kusano et al. [16] reported significant improvements of IKDC, Lysholm, Tegner and VAS scores in 38 patients treated with AMIC procedure with a short-time follow-up of 29 (range, 13 to 51) months. The median defect size was 4.3 cm^2. MRI evaluation showed that tissue filling had occurred, but was generally not complete or homogenous. Pascarella et al. [17] reported significant improvements of IKDC and Lysholm scores in 19 patients with a median follow-up period of 2 (range, 1 to 3) years. The median defect size was 3.6 (2.8 to 3.9) cm^2. Ten (53%)

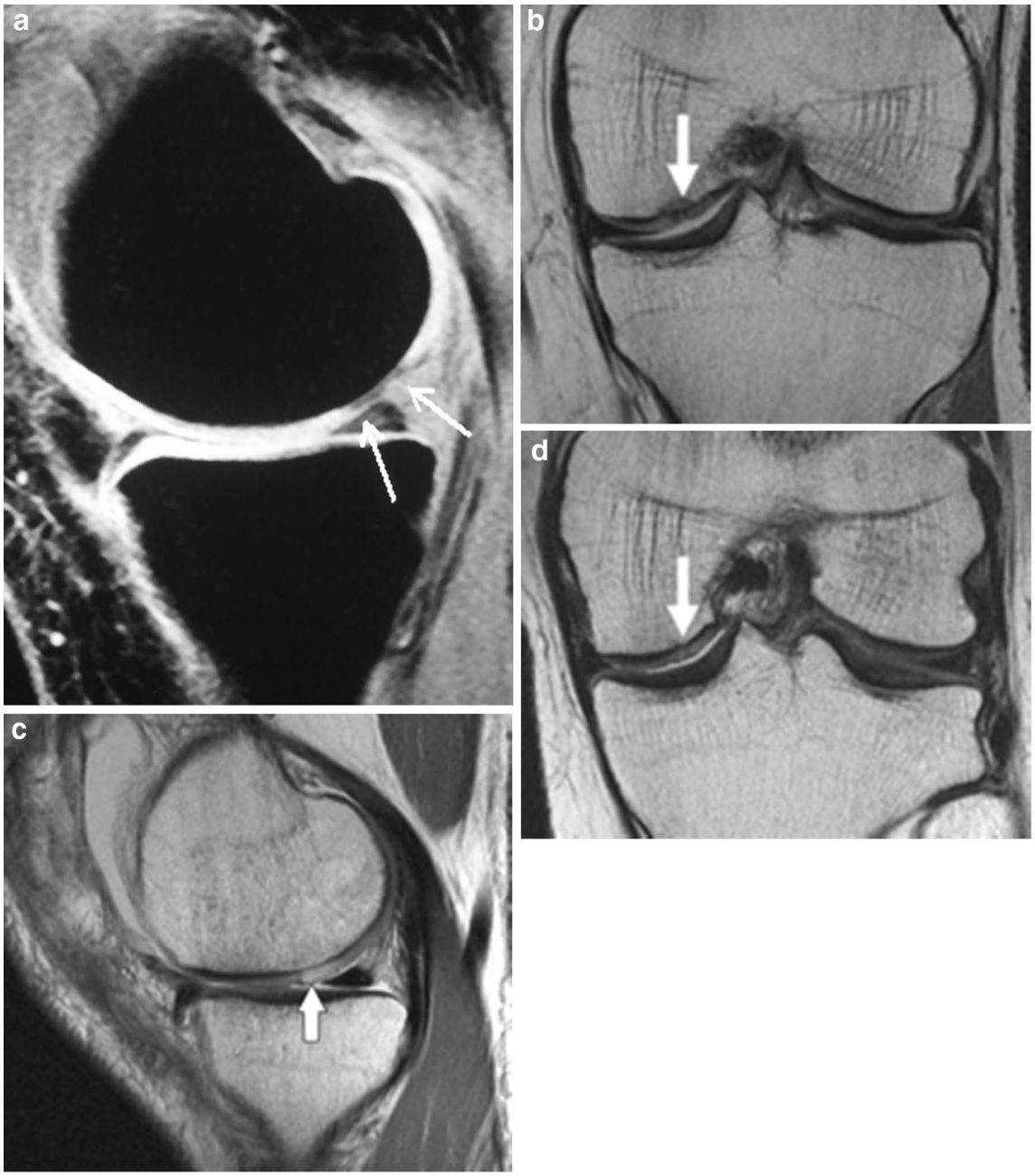

Fig. 2 Preoperative MRI evaluation of a chondral lesion affecting medial femoral condyle (**a, b**). Seven years postoperative MRI evaluation of the same lesion with reduction both of the defect area and subchondral edema (**c, d**)

postoperative MRI showed a significant reduction of the defect area, both in shape, filling, interface and subchondral edema.

The phenomenon of favourable clinical outcomes following cartilage repair procedures that are not supported by the MRI findings has been reported by other investigators [8, 12, 16, 17]. Specifically, Dhollander et al. [8] reported that a satisfying clinical improvement became apparent during the 24 months of follow-up after the AMIC procedure, whereas a slight tendency of deterioration of the repair tissue was observed on MRI during the same period. In the present case series, the subjective satisfaction rate was good or excellent in most (76.2%) of patients, and MRI indicators for poor outcome, such as thickening of the subchondral layer, bony overgrowth or the formation of subchondral cysts, were not observed, although only 66.6% of patients showed good quality repair tissue on MRI.

Compared to other techniques for the treatment of focal full-thickness knee chondral defects, the AMIC technique is a simple and relatively low-cost procedure being performed in a one-step surgery [7], without autologous cartilage grafting or extensive in-vitro cell proliferation. This technique resulted ideal for lesions larger than 2 cm^2 with good long-term results and high patient satisfaction, confirming our initial hypothesis. Arthroscopic approaches of the AMIC technique have been recently published with promising results by Piontek et al. [18] and Sadlik et al. [19] with stable long-term results when compared to arthroscopic microfractures.

The main limitation of this study was the limited cohort of patients. Additionally, tissue repair was analysed only through MRI, and no histological analyses were performed due to ethical considerations. However, to the best of our knowledge, this is the first study describing 7 years follow-up outcomes with the AMIC procedure in the knee. Satisfying clinical and functional results were obtained in most of patients despite the presence of large (2.5–8.0 cm^2) chondral defects. The clinical relevance of this study was that a significant improvement of IKDC and Lysholm scores was obtained in 21 patients treated with AMIC procedure for focal full-thickness knee chondral defects larger than 2 cm^2. Additionally, unlike the isolated microfracturing technique, whose durability over time has been strongly questioned [3, 14], pain reduction and knee function recovery which was maintained over time until to a mean follow-up of 7 years.

Conclusions

The AMIC procedure was shown to be an effective treatment for symptomatic, full-thickness knee chondral defects larger than 2 cm^2. Patients treated with this technique demonstrated significant clinical and functional improvement that was maintained through an average 7-year follow-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Anders S, Volz M, Frick H, Gellissen J (2013) A randomized, controlled trial comparing autologous matrix-induced chondrogenesis (AMIC®) to microfracture: analysis of 1- and 2-year follow-up data of 2 centers. Open Orthop J 3:133–143
2. Arøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG, Engebretsen L (2004) Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med 32:211–215
3. Bae DK, Song SJ, Yoon KH, Heo DB, Kim TJ (2013) Survival analysis of microfracture in the osteoarthritic knee-minimum 10-year follow-up. Arthroscopy 29:244–250
4. Bark S, Piontek T, Behrens P, Mkalaluh S, Varoga D, Gille J (2014) Enhanced microfracture techniques in cartilage knee surgery: fact or fiction? World J Orthop 18:444–449
5. Bedi A, Feeley BT, Williams RJ (2010) Management of articular cartilage defects of the knee. J Bone Joint Surg Am 92:994–1009
6. Benthien JP, Behrens P (2010) Autologous matrix-induced chondrogenesis (AMIC). A one-step procedure for retro - patellar articular resurfacing. Acta Orthop Belg 76:260–263
7. De Girolamo L, Bertolini G, Cervellin M, Sozzi G, Volpi P (2010) Treatment of chondral defects of the knee with one step matrix-assisted technique enhanced by autologous concentrated bone marrow: In vitro characterisation of mesenchymal stem cells from iliac crest and subchondral bone. Injury 41:1172–1177
8. Dhollander A, Moens K, Van der Maas J, Verdonk P, Almqvist KF, Victor J (2014) Treatment of patellofemoral cartilage defects in the knee by autologous matrix-induced chondrogenesis (AMIC). Acta Orthop Belg 80:251–259
9. Enea D, Cecconi S, Calcagno S, Busilacchi A, Manzotti S, Gigante A (2015) One-step cartilage repair in the knee: collagen-covered microfracture and autologous bone marrow concentrate: a pilot study. Knee 22:30–35
10. Flanigan DC, Harris JD, Trinh TQ, Siston RA, Brophy RH (2010) Prevalence of chondral defects in athletes' knees: a systematic review. Med Sci Sports Exerc 42:1795–1780
11. Gille J, Behrens P, Volpi P, de Girolamo L, Reiss E, Zoch W, Anders S (2013) Outcome of autologous matrix induced chondrogenesis (AMIC) in cartilage knee surgery: data of the AMIC Registry. Arch Orthop Trauma Surg 133:87–93
12. Gille J, Schuseil E, Wimmer J, Gellissen J, Schulz AP, Behrens P (2010) Mid-term results of autologous matrix induced chondrogenesis for treatment of focal cartilage defects in the knee. Knee Surg Sports Traumatol Arthrosc 18:1456–1464
13. Gomoll AH, Madry H, Knutsen G, van Dijk N, Seil R, Brittberg M, Kon E (2010) The subchondral bone in articular cartilage repair: current problems in the surgical management. Knee Surg Sports Traumatol Arthrosc 18:434–447
14. Goyal D, Keyhani S, Lee EH, Hui JH (2013) Evidence-based status of microfracture technique: a systematic review of level I and II studies. Arthroscopy 29:1579–1588
15. Kon E, Filardo G, Di Matteo B, Perdisa F, Marcacci M (2013) Matrix assisted autologous chondrocyte transplantation for cartilage treatment. Syst Rev Bone Joint Res 2: 18–25
16. Kusano T, Jakob RP, Gautier E, Magnussen RA, Hoogewoud H, Jacobi M (2012) Treatment of isolated chondral and osteochondral defects in the knee by autologous matrix induced chondrogenesis (AMIC). Knee Surg Sports Traumatol Arthrosc 20:2105–2111
17. Pascarella A, Ciatti R, Pascarella F, Latte C, Di Salvatore MG, Liguori L, Iannella G (2010) Treatment of articular cartilage lesions of the knee joint using a modified AMIC technique. Knee Surg Sports Traumatol Arthrosc 18:509–513
18. Piontek T, Ciemniewska-Gorzela K, Szulc A, Naczk J, Słomczykowski M (2012) Allarthroscopic AMIC procedure for repair of cartilage defects of the knee. Knee Surg Sports Traumatol Arthrosc 20:922–925

19. Sadlik B, Wiewiorski M (2015) Implantation of a collagen matrix for an AMIC repair during dry arthroscopy. Knee Surg Sports Traumatol Arthrosc 23:2349–2352
20. Schiavone Panni A, Cerciello S, Vasso M (2011) The manangement of knee cartilage defects with modified AMIC technique: preliminary results. Int J Immunopathol Pharmacol 24(1 Suppl 2):149–152
21. Williams SK, Amiel D, Ball ST, Allen RT, Tontz WL Jr, Emmerson BC, Badlani NM, Emery SC, Haghighi P, Bugbee WD (2007) Analysis of cartilage tissue on a cellular level in fresh osteochondral allograft retrievals. Am J Sports Med 35:2022–2032