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EXPERIMENTAL STUDY

Cell-free collagen type I matrix for repair of cartilage defects—clinical and magnetic resonance imaging results

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Abstract
Purpose Several well-described techniques are available for the treatment of chondral and osteochondral defects. The aim of the study was to assess the efficacy of a single-stage procedure incorporating a new cell-free collagen type I gel for the treatment of small chondral and osteochondral defects in the knee evaluated at 2-year follow-up.
Methods Fifteen patients were treated with a cell-free collagen type I gel matrix of 11 mm diameter. The grafts were implanted in the debrided cartilage defect and fixed by press-fit only. The clinical outcome was assessed preoperatively and at 6 weeks, and 6, 12 and 24 months after surgery using the International Knee Documentation Committee (IKDC) score, Tegner activity scale and visual analogue scale (VAS). Graft attachment rate was assessed 6 weeks postoperatively using magnetic resonance imaging (MRI). Cartilage regeneration was evaluated using the Magnetic Observation of Cartilage Repair Tissue (MOCART) score at 6, 12 and 24 months after implantation. Clinical results were correlated with MRI findings.
Results Six male and nine female patients were included in this study, with a mean age of 26 (range: 19–40). No complications were reported. The mean VAS values after 6 weeks and the mean IKDC patient values after 6 months were significantly improved from the preoperative values ($P = 0.005$ and $P = 0.009$, respectively). This improvement remained up to the latest follow-up. There were no significant differences between the median preoperative and postoperative Tegner values (n.s.). Significant improvement of the mean MOCART score was observed after 12 months and remained by 24 months ($P < 0.001$). MR images showed that in 14 of the 15 patients, the graft was completely attached by 6 weeks postoperatively. At 24 months after implantation, MRI demonstrated complete filling in all cases with a mainly smooth surface, complete integration of the border zone, homogenous structure of the repaired tissue and nearly normal signal intensity. No correlation between any variables of the MOCART score and the clinical scores was observed.
Conclusions The present study reveals that the new method produces both good clinical and magnetic resonance imaging results. Use of press-fit only implanted grafts of a smaller diameter leads to a high attachment rate at 24-month follow-up.
Level of evidence IV.

Keywords Cartilage repair · Magnetic resonance imaging · MOCART · Clinical outcome · Cell-free collagen type I · Knee

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Introduction

Articular cartilage defects can be treated by a variety of reparative approaches, including bone marrow–stimulating

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techniques and osteochondral transfer [15, 36]. However, there is no evidence regarding which method is superior, and all have inherent problems [3]. To overcome some of these specific problems, tissue engineering techniques have become an important aspect of therapy for cartilage defects. One such technique is autologous chondrocyte implantation (ACI), as introduced by Brittberg et al. [7] in 1987. First-generation ACI, using periosteal flaps, had several potential disadvantages, including periosteal hypertrophy, loss of cells, complexity of the surgical technique and a high revision rate [14, 28]. Therefore, various scaffolds have been developed to overcome some of these problems. Among these, collagen-based matrices are some of the most popular in clinical use [18]. Further development of this approach has led to matrix-induced autologous chondrocyte implantation (MACI), a combination of cultured chondrocytes with 3-dimensional scaffolds [9]. Although MACI represents a well-established and acknowledged therapy with promising clinical results [4, 27], it is a two-step procedure with high costs, is time-consuming and causes donor-site morbidity due to chondrocyte harvesting. In recent years, there has been increasing interest in cell-free repair approaches. More recently, a new cell-free collagen type I gel (CaReS®-1S, Arthro Kinetics, Krems/Donau, Austria) has been introduced for the treatment of smaller local cartilage defects. This cell-free matrix is already in clinical use, serving as a carrier for chondrocytes, similar to MACI [2]. The cell-free technique relies on the potential of cell migration into the matrix leading to cartilage repair. Migration of articular chondrocytes has been reported in vivo and in vitro [25]. However, there are no clinical results available concerning the value of this new device alone.

The aim of this study was to evaluate the efficacy of the cell-free collagen type I matrix for the repair of small diameter chondral defects, using clinical and noninvasive MRI assessment. The hypothesis of the present study was that the cell-free collagen type I matrix triggers chondrocyte in-growth, leading to cartilage repair.

Materials and methods

This is a prospective case series of patients recruited from the Department of Orthopaedics and Rheumatology of the University Hospital, Marburg. The study was performed in accordance with the Helsinki Declaration and was authorised by the local research and ethics committee of the University Hospital, Marburg. All patients gave written informed consent to clinical and MRI follow-up before participation.

Patients were included if they were 18–50 years of age with contained, symptomatic articular cartilage defects of grades III and IV according to International Cartilage Repair Society (ICRS) classification [8] and a defect size <11 mm diameter. Exclusion criteria included ligamentous instability, resection of >1/3 of the meniscus, knee joint malalignment (>5°), inflammatory disease, kissing lesions and articular cartilage degeneration in other compartments.

From 2008 to 2009, 15 patients (six male, nine female) with a mean age of 26 ± 8 years (range: 19–40) were included. Ten procedures were performed in the right knee, and 5 in the left knee. The chondral defects were mapped on both the frontal and the sagittal views on the medial femoral condyle in 8 (7 central/central; 1 central/posterior), the lateral femoral condyle in 3 (3 central/central) and on the retropatellar surface in 4 (3 medial/central; 1 medial/distal) cases. The aetiology of the chondral lesions was traumatic origin in 8 patients, idiopathic in 3 patients and due to aseptic necrosis of the subchondral bone in 4 patients. When performing the implantation of the cell-free matricies, concomitant reconstruction of the medial patellofemoral ligament [33] due to patella instability was performed in 2 cases.

Cell-free collagen type I gel (CaReS-1S®)

The matricies were made of a three-dimensional cell-free collagen gel consisting of 4.8 mg/mL type I collagen from the tails of rats, which is already in clinical use. The diameter of the matricies was 11 mm and, depending on the depth of the defect, had a thickness of 4 or 6 mm. The matricies were stored in sterile phosphate-buffered saline solution and preserved at 4°C until use.

Surgical procedure

All operations were carried out by a single surgeon (TE). Using standard arthroscopic portals, diagnostic arthroscopy was performed to confirm that the patient fitted the inclusion/exclusion criteria and to identify any further intra-articular abnormalities. The width of the chondral defect was measured with an arthroscopic ruler. When the defect met the inclusion criteria, a mini-arthrotomy was performed to expose the defect in the specific compartment. The chondral defect was carefully prepared using an 11-mm-diameter cutter and a sharp angulated curette, down to, and avoiding penetration of, the subchondral bone. In cases where an osteochondral defect was found, a deep debridement of the sclerotic subchondral bone was performed, followed by press-fit filling of the defect with autologous cancellous bone from the proximal tibia. Generally, on the retropatellar surface, an 11 × 6 mm graft was used, and on the femoral condyle, an 11 × 4 mm graft was used. The collagen type I gel was directly pushed into

the defect with an 11-mm stamp, and no additional fixation technique was used. The graft was considered to be sufficient when the matricies matched exactly the geometry of the prepared defect, and complete congruity with the surrounding cartilage rim was achieved. The knee joint was held in an extended position for 3 min before the joint was flexed three times to ensure sufficient fixation of the grafts. Finally, the mini-arthrotomy was closed in a standard fashion and a sterile compression dressing applied. Any surgical complications were recorded.

Postoperative rehabilitation

Postoperatively, all knee joints were fixed for 2 days in a hinged knee brace locked in extension. The patients were allowed to move using two crutches with toe-touch weight bearing. The rehabilitation programme was different for graft implantation on the retropatellar surface compared with the femoral condyle, which followed a standardised regimen. Patients received the cell-free matricies on the femoral condyle were allowed to use continuous passive motion (CPM) at the third postoperative days in a range of 0–0–30 during the first week. Patients received the cell-free matricies on the retropatellar were allowed to use CPM at the third postoperative days in a range of 0–0–30 for the first 3 weeks. Between week 4 and 6, an increase in load and knee flexion was allowed, followed by the progression to full load and no limitation of knee flexion after 6 weeks. Six months after implantation, the patients returned to their former activity levels, including cycling or jogging.

Outcome measures

Clinical evaluation

Data collection was performed preoperatively and after 6 weeks and 6, 12 and 24 months postoperatively using the subjective International Knee Documentation Committee (IKDC) score [17], Tegner activity scale [37] and visual analogue score (VAS) [11].

Magnetic resonance images

The follow-up MRI examination was carried out using a standardised protocol at postoperative time-points of 6 weeks and 6, 12 and 24 months. Six weeks after the procedure, MRI was performed to evaluate the early postoperative adherence rate of the grafts, using a scoring system described by Marlovits et al. [23]. This system grades the transplants as completely attached, partially attached or detached. Completely attached was defined as the absence of any visible fissure/gaps between the grafts and the surrounding cartilage. In partial detachment, the graft only covered a part of the defect. If the cartilage defect floor was completely empty, this was classified as detachment. The validity and the reliability of this scoring system have been proven [23]. Further MR imaging was performed for description of the repair tissue using the MOCART (Magnetic resonance observation of cartilage repair tissue) score [22]. The cell-free scaffold was assessed for the following nine parameters: degree and filling of the defect; integration at the border zone; structure and signal intensity of repair tissue; surface of the repair tissue, determined in two different sequences; the constitution of the subchondral bone and lamina; and the existence of adhesions and effusions. The maximum score achievable based on the evaluation of these 9 variables is 100.

All MR images were obtained with a 1.5-Tesla MRI Scanner MAGNETOM Espree (Siemens, Erlangen, Germany). A knee coil with a field of view of 18 cm was used with the knee positioned in extension. The following standardised sequences were recorded for coronal, sagittal and transverse slice orientations: proton density turbo-spin-echo fast suppression (320 × 320; thickness 3 mm; repeat time (TR) 3,000 ms; echo time (TE) 37 ms); T1 (384 × 384; thickness 3 mm; TR 411 ms; TE 13 ms); T1-volume-interpolated breathhold examination (280 × 320; thickness 1.5 mm, TR 16; TE 7); and T2 (512 × 512; thickness 3 mm; TR 460 ms; TE 15 ms). All MR images were assessed by a senior musculoskeletal radiologist (MR).

Statistical analysis

The paired *t* test was performed for the IKDC score and the VAS to compare pre- and postoperative values. Data are expressed as means with standard deviations. The non-parametric Wilcoxon-signed rank test was performed for the Tegner activity scale to compare pre- and postoperative values. Data are expressed as medians and interquartile ranges. For the MOCART score, paired *t* tests for changes in values after 6 weeks were carried out. To identify any relationships between the variables of the MOCART score and the clinical scores (IKDC, VAS, Tegner) at different follow-up times, the Pearson product moment correlation was performed. For all tests, $P < 0.05$ was considered significant. The statistical software package SAS (Version 9.2) was used for biometric analysis.

Results

All patients completed the 24-month clinical and MRI evaluation. The implantation of the cell-free graft was successful in all patients. No displacement of the graft was observed intra-operatively after moving the knee through a

range of motion three times. No patient-related complications nor device-related complications were encountered. All patients followed the standardised rehabilitation programme.

Clinical outcome

All of the clinical outcome scores showed an improvement from preoperative values. The difference between the mean subjective IKDC score at baseline and 24 months postoperatively was significant ($P = 0.009$; Fig. 1). The median Tegner activity scale showed no significant differences between the baseline 3 (range: 1–4) and postoperative values 4 (range: 2–4) at the latest follow-up (n.s.), including involvement in moderately heavy work and recreational sports. For the mean VAS, the difference between baseline and 24 months postoperatively was significant ($P = 0.006$; Fig. 2). One patient suffered severe pain indicated by the VAS after MPFL reconstruction at the latest follow-up; however, IKDC showed a score of 68.

MRI results

Using the MOCART scoring system, there was significant differences between baseline and 24 months postoperatively ($P < 0.001$; Fig. 3). There was no strong correlation between the MOCART score and any of the clinical outcomes.

At 6-week follow-up, a completely attached graft was found in 14 of the 15 patients. In one case, a partially detached graft was noticed. An improvement from partially detached to completely attached graft could be observed at the 12-month follow-up. No subchondral bone was exposed, but this was considered a fixation failure.

At the latest follow-up, all patients showed complete defect filling. The integration to the border zone was complete in 14 patients, but incomplete in one of the patients as a split demarcating the graft–host border was present. The surface of the repair tissue was smooth in 9 cases and irregular in 6 cases. Homogeneous repair tissue was observed in 7 patients, and the signal intensity of the repair tissue was normal or nearly normal in all cases. In the four lesions which were osteochondral, the subchondral lamina was not intact, but the subchondral bone was shown to be intact after cancellous bone grafting in all cases.

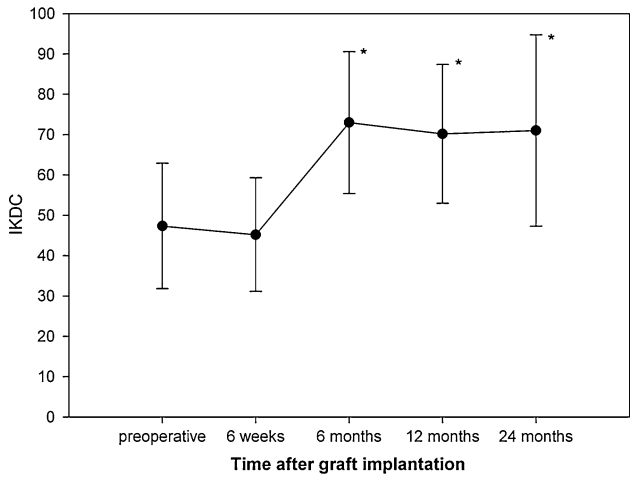

Fig. 1 Clinical outcome evaluated with the IKDC score. Scores are indicated as mean with SD. *Asterisks* indicate a statistically significant difference on paired *t* test ($P < 0.05$) compared with the preoperative values

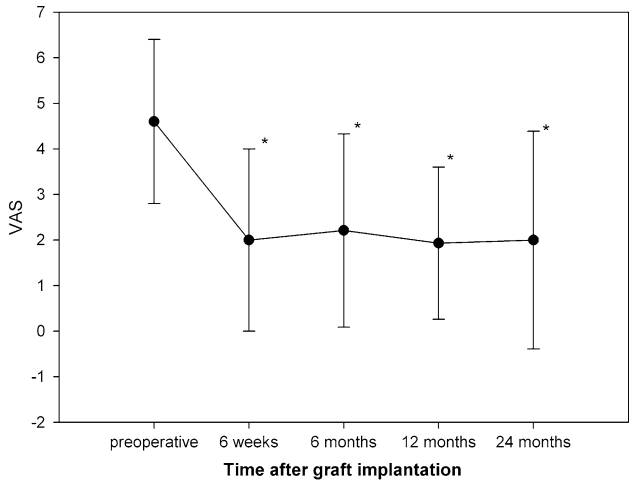

Fig. 2 Clinical outcome evaluated with the VAS. Scores are indicated as mean with SD. Statistical analysis was performed using paired *t* test. The *asterisks* indicate a statistically significant difference ($P < 0.05$) compared with the preoperative situation

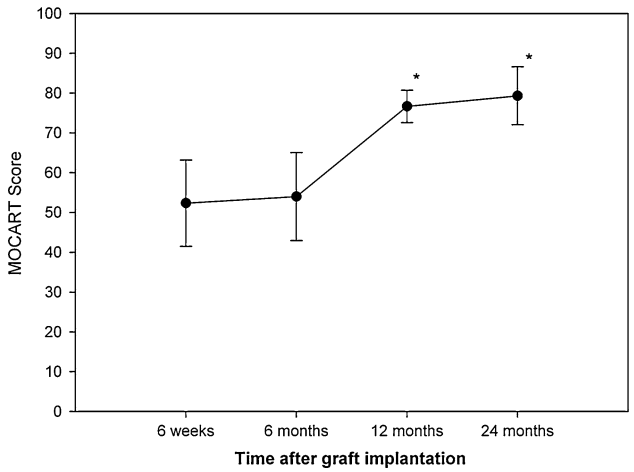

Fig. 3 MOCART score over a period of 24 months after implantation of the cell-free collagen type I gel. Scores are indicated as mean with SD. The *asterisks* indicate a statistically significant difference ($P < 0.05$) compared with the MOCART score 6 weeks postoperatively

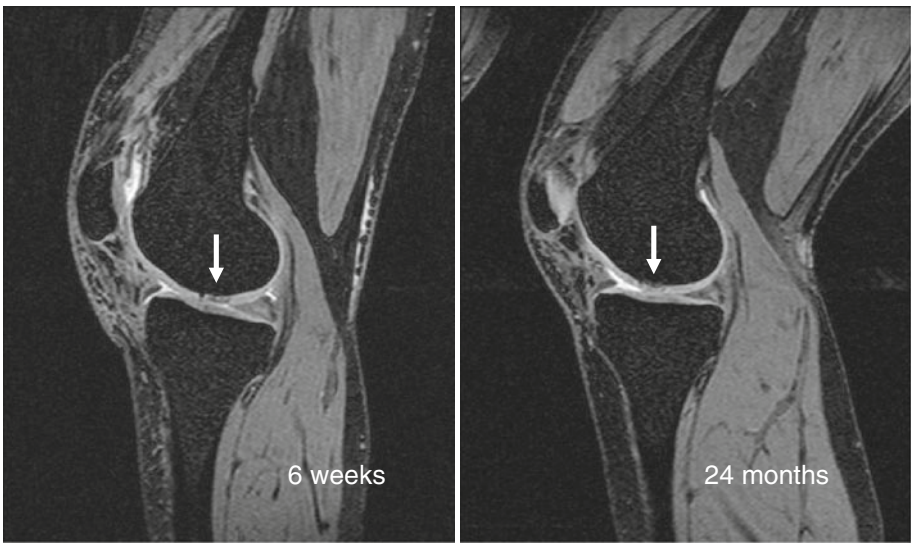

Fig. 4 Magnetic resonance images of a 25-year-old female patient. The graft in the medial femoral condyle (*white arrow*) is completely attached after 6 weeks postoperatively. At 24 months, the surface is intact, and the structure and the signal intensity show some alterations

Adhesions could not be detected, but effusions were found in 3 patients. In two knees, a new meniscal lesion and one subchondral cyst could be found. Representative MR images of 1 patient are shown in Fig. 4.

Discussion

The most important finding of the present study was that the cell-free collagen type I matrix has supported a reparative response, leading to cartilage repair.

Although the defects included in this study are of small diameter, all of the patients failed extensive nonsurgical management before surgical intervention. A number of techniques have been described to address small cartilage defects. Bone marrow–stimulating techniques such as microfracture have produced satisfactory results [24]; however, some studies have shown a deterioration in clinical outcome at mid-term follow-up, thought to be related to the inferior biomechanical quality of fibrocartilaginous repair tissue [13]. Osteochondral autologous transplantation utilises the immediate transfer of hyaline cartilage; however, this technique is associated with technical difficulties, donor-site morbidity, limited graft availability and lack of cartilage integration [6]. Other procedures have been developed, which implant cell-free scaffolds; however, these rely on microfracture as a cell source, such as matrix-induced autologous chondrogenesis [5] and BST Cargel [16]. The question of which cell source is optimal remains and requires future investigation. To overcome some of these limitations, the new collagen gel may present an alternative to recent cartilage repair approaches in the treatment of small cartilage defects. The basic principle of the cell-free collagen type I matrix is to fill the cartilage defect with a matrix structure, providing a scaffold for chondrocytes to migrate from the perilesional tissue, enabling attachment, proliferation and extracellular matrix production. Migration of chondrocytes has been reported in vivo and in vitro [25], and collagen-based matricies have the capacity to promote chondrocyte proliferation and proteoglycan synthesis in vitro [40].

Some previous studies have investigated the question of repair tissue quality after implantation of a cell-free gel as was used in this study. Schneider et al. [32] investigated the new graft in a Goettinger minipig-based model and compared the results with a cell-based procedure (MACI) or abrasion arthroplasty. They noticed that after 6 weeks, chondrocyte-like cell migration into the initially cell-free gel had occurred. After 12-month follow-up, the repair tissue quality was equal to that achieved using a cell-based procedure. The high chondrogenic potential of the cell-free gel could be confirmed in a nude mouse model [12]. Schagemann et al. [31] investigated the suitability of cell-laden and cell-free alginate-gelatin biopolymer hydrogel for osteochondral restoration in a sheep model and also observed cellular in-growth into the initially cell-free scaffold. However, whether such in vitro results can be transformed to in vivo outcome remains unclear.

Safe fixation of tissue-engineered constructs is important to achieve good clinical results [34]. Gel-like matrices for cartilage repair are fixed either using fibrin glue or by press fitting [26, 29]. In the present study, the small matricies were fixed by press-fit only, without using any further fixation techniques. Vertical edges of the surrounding healthy cartilage were fashioned to achieve a stable rim and to avoid lateral expansion of the matrix. In 14 of 15 patients, a sufficient adherence rate with completely attached grafts was noticed 6 weeks postoperatively. These findings are consistent with a previous ex vivo cartilage repair model study, showing that the press-fit fixation technique leads to similar fixation quality as fibrin

glue when used with cell-free collagen gels as used in the present study [10]. However, for larger matricies, the additional use of fibrin glue may be more favourable to improve the mechanical stability of the scaffolds.

Various studies have shown that good clinical results can be obtained when cartilage defects located on the femoral condyle are repaired, regardless of the surgical technique [20, 30]. Conversely, patellofemoral cartilage lesions show a substantially lower proportion of good results with associated high complication rate. Niemeyer et al. demonstrated a higher incidence of hypertrophy of regenerated cartilage on the patella than on the femoral condyles when using autologous chondrocyte implantation [28]. In the present study, MRI evaluation showed no hypertrophy of regenerated cartilage on the patella.

MRI has become a valuable tool for the assessment of cartilage repair techniques because of good soft tissue contrast, accurate demonstration of articular cartilage and multiplanar capability [1]. Despite these advantages, MRI is not able to show the composition of the cartilage repair tissue [38]. Histological biopsies are the gold standard after cartilage repair approaches [42]. However, since MRI and cartilage evaluating protocols (MOCART) showed good morphological quality of the repair tissue in the present study, no biopsy was performed to assess the quality of the repair tissue in vivo.

The MOCART score is a well-established system for assessing articular cartilage repair tissue [22]. Welsch et al. [41] reported a mean MOCART score of 75 and 75.5 after microfracture and MACI, respectively, with a mean follow-up of 29 months. Trattnig et al. [39] reported a mean score of 73 after 12 months using the MACI procedure. Correlations between clinical outcome and MRI appearance have been noticed [22, 24]. In the present study, the mean MOCART score was 76 after 12 months and 79 after 24 months. A strong correlation between the MOCART score and the clinical outcome could not be detected. However, a direct comparison with these studies is only possible to a certain degree, due to inherent differences in study population, defect size, follow-up time and basic biological approach. The MRI evaluation showed in the present study that in the majority of the cases, there was an improvement from incomplete filling of the defect at 6 months postoperatively, to complete defect filling at latest follow-up. This may demonstrate the potential of implant in-growth from the host tissue. Twenty-four months after cell-free matrix implantation, 1 patient was newly diagnosed with subchondral cysts. The reason for this can only be speculated. There may be some persistent small gaps between the graft and the native cartilage, so that synovial fluid can reach the subchondral bone plate and result in a persistent stimulus. However, the cysts were not associated with any pain. At the latest follow-up, the signal characteristics of the repair tissue were different from those of the original native cartilage in all cases. It is accepted that cartilage regeneration and tissue remodelling take years after implantation [19] and cartilage remodelling is visible on MRI [21]. Therefore, studies with longer follow-up are required to gather more information about the maturation process.

As yet, no mid-term results have been published concerned with the cell-free collagen I matrix. Andereya et al. [2] reported the first clinical experience with the matrix as used in the present study, but instead seeded with autologous chondrocytes (CaReS®). Twenty-two patients with chondral and osteochondral femoral lesions with a mean defect size of 6 cm^2 were treated and 2-year follow-up reported. Short-term results showed significant improvements in each of the different outcome parameters. In the current study, the clinical scores showed an overall improvement 24 months after implantation. This indicates that there is an improvement in the loading and functionality of the knee. Both IKDC and VAS pain scores showed significant differences in comparison with preoperative values, whereas the Tegner activity scale increased more over time but failed to show statistical significance. We are aware that no definitive conclusion regarding the possible benefit of cell-free matricies, in comparison with matricies seeded with cells, can be drawn from the present study. A direct comparison of the results between cell-free and cell-seeded matrices would be beneficial; however, this study does demonstrate satisfying results when this new device is used in this manner. Other repair techniques such as bone marrow stimulation [13] and osteochondral transfer [35] show the most substantial improvements within the first 2 years. However, the results have been shown to deteriorate after 2 years [24]. Therefore, further clinical investigations are needed to evaluate the value of cell-free implants over time.

The present study has some limitations. Firstly, only 2-year results are presented. Even though the early clinical and MRI results are promising, a final conclusion about the value of the cell-free collagen type I device cannot be drawn. However, as the treatment of cartilage defects with cell-free collagen gels evolves, these results can be used as the basis for further studies dealing with this technique. Secondly, our findings are based on a small sample size. Before widespread use of this technique, further clarification of the mid-term results are required. Finally, the treated cartilage defect size was small. Nevertheless, even for these symptomatic, contained, small-sized defects, the optimal therapy should be identified.

Conclusion

Cell-free collagen type I matrix repair of small articular cartilage lesions in the knee leads to good clinical results at

a follow-up of 2 years. A sufficient adherence rate and articular resurfacing were detected by MRI. The new collagen type I matrix might help to overcome some of the disadvantages inherent in conventional cartilage tissue engineering techniques.

Conflict of interest TE and MDS are consultants to Smith & Nephew, Arthroscopy, Germany. The Magnetic Resonance Imaging was supported by a research fund of Arthro Kinetics.

References

1. Alparslan L, Minas T, Winalski CS (2001) Magnetic resonance imaging of autologous chondrocyte implantation. Semin Ultrasound CT MR 22:341–351
2. Andereya S, Maus U, Gavenis K, Muller-Rath R, Miltner O, Mumme T, Schneider U (2006) First clinical experiences with a novel 3D-collagen gel (CaReS) for the treatment of focal cartilage defects in the knee. Z Orthop Ihre Grenzgeb 144:272–280
3. Bae DK, Yoon KH, Song SJ (2006) Cartilage healing after microfracture in osteoarthritic knees. Arthroscopy 22:367–374
4. Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J (2010) Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 18:519–527
5. Benthien JP, Behrens P (2011) The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. Knee Surg Sports Traumatol Arthrosc 19:1316–1319
6. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, Skinner JA, Pringle J (2003) A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 85:223–230
7. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331:889–895
8. Brittberg M, Winalski CS (2003) Evaluation of cartilage injuries and repair. J Bone Joint Surg Am 85-A(Suppl 2):58–69
9. Cherubino P, Grassi FA, Bulgheroni P, Ronga M (2003) Autologous chondrocyte implantation using a bilayer collagen membrane: a preliminary report. J Orthop Surg (Hong Kong) 11:10–15
10. Efe T, Fuglein A, Heyse TJ, Stein T, Timmesfeld N, Fuchs-Winkelmann S, Schmitt J, Paletta JR, Schofer MD (2011) Fibrin glue does not improve the fixation of press-fitted cell-free collagen gel plugs in an ex vivo cartilage repair model. Knee Surg Sports Traumatol Arthrosc. doi:10.1007/s00167-011-1571-4
11. Flandry F, Hunt JP, Terry GC, Hughston JC (1991) Analysis of subjective knee complaints using visual analog scales. Am J Sports Med 19:112–118
12. Gavenis K, Schmidt-Rohlfing B, Andereya S, Mumme T, Schneider U, Mueller-Rath R (2010) A cell-free collagen type I device for the treatment of focal cartilage defects. Artif Organs 34:79–83
13. Gobbi A, Nunag P, Malinowski K (2005) Treatment of full thickness chondral lesions of the knee with microfracture in a group of athletes. Knee Surg Sports Traumatol Arthrosc 13:213–221
14. Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A (2006) A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: periosteum covered versus type I/III collagen covered. Knee 13:203–210
15. Hangody L, Vasarhelyi G, Hangody LR, Sukosd Z, Tibay G, Bartha L, Bodo G (2008) Autologous osteochondral grafting—technique and long-term results. Injury 39(Suppl 1):332–339
16. Hoemann CD, Hurtig M, Rossomacha E, Sun J, Chevrier A, Shive MS, Buschmann MD (2005) Chitosan-glycerol phosphate/blood implants improve hyaline cartilage repair in ovine microfracture defects. J Bone Joint Surg Am 87:2671–2686
17. Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, Richmond JC, Shelborne KD (2001) Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 29:600–613
18. Iwasa J, Engebretsen L, Shima Y, Ochi M (2009) Clinical application of scaffolds for cartilage tissue engineering. Knee Surg Sports Traumatol Arthrosc 17:561–577
19. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Krause S, Ossendorf C, Meier D, Ghanem N, Uhl M (2007) Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. Am J Sports Med 35:1261–1268
20. Kreuz PC, Steinwachs MR, Erggelet C, Krause SJ, Konrad G, Uhl M, Sudkamp N (2006) Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthr Cartil 14:1119–1125
21. Marlovits S, Mamisch TC, Vekszler G, Resinger C, Trattnig S (2008) Magnetic resonance imaging for diagnosis and assessment of cartilage defect repairs. Injury 39(Suppl 1):13–25
22. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S (2006) Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol 57:16–23
23. Marlovits S, Striessnig G, Kutscha-Lissberg F, Resinger C, Aldrian SM, Vecsei V, Trattnig S (2005) Early postoperative adherence of matrix-induced autologous chondrocyte implantation for the treatment of full-thickness cartilage defects of the femoral condyle. Knee Surg Sports Traumatol Arthrosc 13:451–457
24. Mithoefer K, Williams RJ 3rd, Warren RF, Potter HG, Spock CR, Jones EC, Wickiewicz TL, Marx RG (2005) The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Joint Surg Am 87:1911–1920
25. Morales TI (2007) Chondrocyte moves: clever strategies? Osteoarthr Cartil 15:861–871
26. Nehrer S, Domayer S, Dorotka R, Schatz K, Bindreiter U, Kotz R (2006) Three-year clinical outcome after chondrocyte transplantation using a hyaluronan matrix for cartilage repair. Eur J Radiol 57:3–8
27. Niemeyer P, Lenz P, Kreuz PC, Salzmann GM, Sudkamp NP, Schmal H, Steinwachs M (2010) Chondrocyte-seeded type I/III collagen membrane for autologous chondrocyte transplantation: prospective 2-year results in patients with cartilage defects of the knee joint. Arthroscopy 26:1074–1082
28. Niemeyer P, Pestka JM, Kreuz PC, Erggelet C, Schmal H, Suedkamp NP, Steinwachs M (2008) Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. Am J Sports Med 36:2091–2099
29. Pavesio A, Abatangelo G, Borrione A, Brocchetta D, Hollander AP, Kon E, Torasso F, Zanasi S, Marcacci M (2003) Hyaluronan-based scaffolds (Hyalograft C) in the treatment of knee cartilage defects: preliminary clinical findings. Novartis Found Symp 249:203–217
30. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A (2002) Autologous chondrocyte transplantation. Biomechanics and long-term durability. Am J Sports Med 30:2–12

31. Schagemann JC, Erggelet C, Chung HW, Lahm A, Kurz H, Mrosek EH (2009) Cell-laden and cell-free biopolymer hydrogel for the treatment of osteochondral defects in a sheep model. Tissue Eng Part A 15:75–82
32. Schneider U, Schmidt-Rohlfing B, Gavenis K, Maus U, Mueller-Rath R, Andereya S (2011) A comparative study of 3 different cartilage repair techniques. Knee Surg Sports Traumatol Arthrosc. doi:10.1007/s00167-011-1460-x
33. Schottle PB, Fucentese SF, Romero J (2005) Clinical and radiological outcome of medial patellofemoral ligament reconstruction with a semitendinosus autograft for patella instability. Knee Surg Sports Traumatol Arthrosc 13:516–521
34. Sittinger M, Perka C, Schultz O, Haupl T, Burmester GR (1999) Joint cartilage regeneration by tissue engineering. Z Rheumatol 58:130–135
35. Solheim E, Hegna J, Oyen J, Austgulen OK, Harlem T, Strand T (2010) Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. Knee 17: 84–87
36. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG (2003) Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy 19:477–484
37. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res 198:43–49
38. Tins BJ, McCall IW, Takahashi T, Cassar-Pullicino V, Roberts S, Ashton B, Richardson J (2005) Autologous chondrocyte implantation in knee joint: MR imaging and histologic features at 1-year follow-up. Radiology 234:501–508
39. Trattnig S, Ba-Ssalamah A, Pinker K, Plank C, Vecsei V, Marlovits S (2005) Matrix-based autologous chondrocyte implantation for cartilage repair: noninvasive monitoring by high-resolution magnetic resonance imaging. Magn Reson Imaging 23:779–787
40. Uchio Y, Ochi M, Matsusaki M, Kurioka H, Katsube K (2000) Human chondrocyte proliferation and matrix synthesis cultured in Atelocollagen gel. J Biomed Mater Res 50:138–143
41. Welsch GH, Trattnig S, Domayer S, Marlovits S, White LM, Mamisch TC (2009) Multimodal approach in the use of clinical scoring, morphological MRI and biochemical T2-mapping and diffusion-weighted imaging in their ability to assess differences between cartilage repair tissue after microfracture therapy and matrix-associated autologous chondrocyte transplantation: a pilot study. Osteoarthr Cartil 17:1219–1227
42. Zheng MH, Willers C, Kirilak L, Yates P, Xu J, Wood D, Shimmin A (2007) Matrix-induced autologous chondrocyte implantation (MACI): biological and histological assessment. Tissue Eng 13:737–746