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Cell-free cartilage repair in large defects of the knee: increased failure rate 5 years after implantation of a collagen type I scaffold

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Abstract

Introduction Cartilage defects of the knee remain a challenging problem in orthopedic surgery despite the ongoing improvements in regenerative procedures such as the autologous chondrocyte transplantation. Due to the lack of donor-site morbidity and the single-stage procedure cell-free scaffolds are an interesting alternative to cell-based procedures. But as currently mid- and long-term data are lacking, the aim of the present study was to present mid-term clinical, radiological and histological results of a cell-free collagen type I scaffolds for cartilage repair.

Materials and methods Twenty-eight patients were followed prospectively. Clinical evaluation using patient-reported outcome measures (KOOS, IKDC; VAS for pain, Tegner score for activity) as well as radiologic evaluation of the repair tissue (MOCART) was performed at 1 year, 2 years and 5 years. Histologic evaluation of the repair tissue was done in case of revision surgery using the ICRS II score for human cartilage repair.

Results In these large cartilage defects with a mean defect size of $3.7 \pm 1.9\ cm^2$, clinical failure necessitating revision surgery was seen in 5 of 28 patients (18%). While the remaining patients showed good-to-excellent clinical results (KOOS, IKDC, VAS, Tegner), the radiologic appearance of the repair tissue showed a reduction of the MOCART score between the 2- and 5-year follow-up. Histologic evaluation of the repair tissue showed a cartilage-like appearance with no signs of inflammation or cell death but an overall medium tissue quality according to the ICRS II Score.

Conclusion The use of this cell-free collagen type I scaffold for large defects showed increased wear of the repair tissue and clinical failure in 18% of cases at 5-year follow-up.

Keywords Knee · Cartilage repair · Cell free · Collagen · Large defects · Histology · Revision

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Introduction

Chondral defects of the knee, whether as a result of trauma, following meniscal injury or as a degenerative defect, remain a challenging problem [1–3].

Several strategies are currently used to treat chondral defects of the knee's articular cartilage. For smaller defects and less active patients the microfracture procedure (MFX) is advocated [4, 5]. But as the repair tissue generated by this technique is of lesser quality, results are unsatisfactory when larger defects, especially in more active patients, are treated [6, 7]. For these patients, the matrix-induced autologous chondrocyte transplantation (MACT) is favored. But both techniques have important disadvantages. For the microfracture procedure, there is, in addition to the limited tissue quality of the resulting repair tissue, a risk for the formation of intralesional osteophytes or disturbance of the subchondral

architecture [8], which might be responsible for the inferior outcomes of revision autologous chondrocyte transplantation after failed MFX [9, 10].

For the MACT, vital chondrocytes need to be harvested and cultured over time, resulting in possible donor site morbidity, high costs and a two-stage procedure [11].

Another possibility is the use of scaffolds in combination with the microfracture procedure to possibly improve the quality of the resulting repair tissue and thus possibly treat larger defects [12]. But as summarized in recent reviews, high-quality studies with long-term follow-up to support the use of these augmented MFX procedures are currently lacking and these augmented MFX techniques share the same risks as the MFX with regard to injury of the subchondral bone [13, 14].

Due to these reasons, alternative techniques are currently investigated. One possible alternative is the use of cell-free, off-the-shelf scaffolds promoting the formation of repair tissue without the need for MFX. One such scaffold is the collagen type I CaReS-1S® scaffold (CaReS-1S®, Arthro Kinetics AG, Krems/Donau, Austria). Early and mid-term data on small cartilage defects as well as early data on large defects are already available for this scaffold [15–17]. The aim of the present study is to report mid-term follow-up data based on clinical assessment, magnetic resonance imaging and histological evaluation of failed cases.

Methods

A series of 28 patients were followed prospectively after implantation of a collagen type I scaffold. Short-term follow-up results of this cohort were published earlier [16].

Indication for surgery was patient age between 18 and 50 years, cartilage defects ICRS III or IV, a stable knee joint, intact menisci (more than two-thirds of intact substance) and a physiological leg axis (measured clinically). Exclusion criteria were kissing lesions, flexion or extension deficits and inflammatory joint disease. The study was performed in accordance with the Declaration of Helsinki and under the principles of Good Clinical Practice and was approved by the local ethics committee (IRB no. 10/11).

Clinical follow-up by means of patient-reported outcome measures such as the subjective survey of the International Knee Documentation Committee (IKDC) score [18], the Tegner activity scale [19], a visual analogue scale (VAS) for pain [20], the Knee injury and Osteoarthritis Outcome Score (KOOS) [21, 22], a structured clinical examination and radiological follow-up by magnetic resonance imaging with evaluation of the former lesion according to the Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) score [23] was done at 1 year, 2 years and 5 years after surgery.

Surgery

Implantation of the scaffold was done after arthroscopic verification of the indication via mini-arthrotomy. Surgical technique and rehabilitation protocol was described earlier [16]. In short, the mini-arthrotomy was centered over the defect in case of defects of the femoral condyle, or was carried out as a medial or lateral parapatellar incision depending on defect localization on the retro-patellar surface. Defects were measured and stable, intact cartilage borders were created using sharp punches of various diameters and forms. The lesion was debrided down to the subchondral lamina but without damaging the subchondral bone. Five patients were diagnosed with osteochondrosis dissecans. In these cases, debridement included complete removal of the sclerotic bone and bone grafting with autologous bone from the ipsilateral tibial head. The collagen scaffolds were placed on top of the bone grafting in these cases. Scaffolds were cut to the appropriate size from either 4- or 6-mm-thick scaffolds depending on defect localization using the same sharp punches and implanted in a press-fit manner without additional fixation.

All patients were kept in full extension for 48 h after surgery. Further postoperative rehabilitation depended on defect localization. Patients with patellofemoral defects were allowed full weight-bearing with the knee locked in extension but were limited to 30° of flexion for the first 3 weeks.

In case of tibio-femoral defects, patients were kept on crutches with only toe-touch weight-bearing for 4 weeks. Intensive continuous passive motion without load was recommended in all cases.

Histology

Biopsies were taken during reoperation. In case of failure of the cartilage repair, the complete former lesion including a core biopsy could be evaluated. In case of reoperation due to non-cartilage reasons, only a core biopsy was taken arthroscopically. Specimens were directly transferred into a 4% formaldehyde solution for fixation. After standard paraffin embedding, specimens were cut into slices of 5 µm thickness and stained with hematoxylin–eosin and safranin O. Additional immunohistochemistry was performed for collagen type I and collagen type II.

All slices were evaluated by a senior pathologist blinded to the clinical results. Evaluation was carried out using the ICRS II scoring system for histologic assessment of the quality of human cartilage repair [24].

Magnetic resonance imaging

A 1.5-T Magnetom Espree VB17 (Siemens, Erlangen, Germany) was used for image acquisition and detailed MR

sequences for coronal, sagittal and transverse images were reported earlier [16]. In short, proton density fat-suppressed turbospin-echo, T1, T1-weighed volume-interpolated breath-hold examination and T2-weighed images were acquired. All MR images were assessed by a senior musculoskeletal radiologist who was blinded to clinical data. The MOCART score was used to grade all lesions [23].

Statistical analysis

Data were processed using Microsoft® Excel® version 16.11 and IBM® SPSS® statistics version 24. Student's *t* test was used for comparison of pre- and postoperative clinical and radiological scores. The Kaplan–Meier method was used to plot and calculate survival of the implant. Histological results are given in a descriptive manner due to the limited sample sizes. *P* values < 0.05 were considered statistically significant.

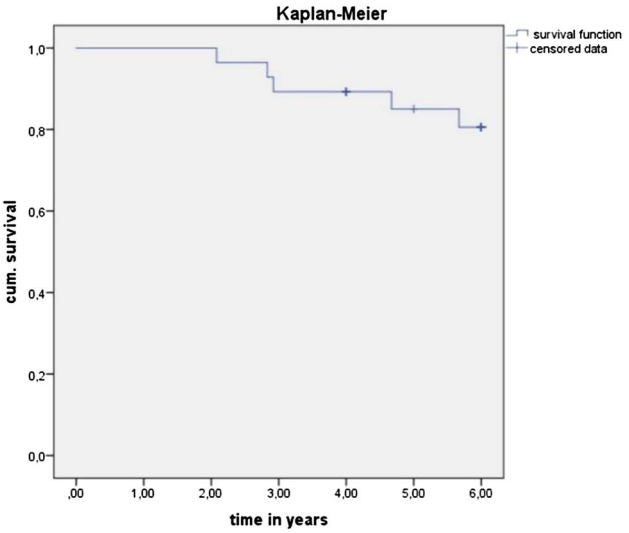

Fig. 1 Kaplan–Meier survival function. At 6 years, 64% of patients were censored. Cumulative survival at 5.7 years was 0.806

Results

Of the initial 28 patients 5 were lost between the 2-year and the final 5-year follow-up, leaving 23 complete data sets for evaluation. Mean cartilage defect size was 3.7 ± 1.9 cm^2 and the medial femoral condyle was the most common defect localisation ($n = 13$). Five patients (18%) had to undergo revision surgery due to symptomatic wear of the former implant with conversion to autologous chondrocyte transplantation (ACT) in four cases and a microfracture procedure in one case because the patient refused the two-staged ACT procedure. Revised defects were localized at the medial femoral condyle in four cases and on the patella in one case. Median time to revision was 2.9 years (range 2.1–5.7 years). The Kaplan–Meier survival graph is given in Fig. 1. At 6 years, 64% of patients were censored. Cumulative survival at 5.7 years was 0.806.

A tendency towards larger defects was found in the failure group when compared to the successful repair group (4.0 cm^2 vs. 3.2 cm^2), although without statistical significance ($p = 0.26$). No significant differences between failure and successful repair group were also found regarding age at the time of surgery (31.3 years vs. 35.6 years) or BMI (26.3 vs. 27.8). An overview of both groups is given in Table 1 (Table 1).

Within the group of successful repairs, clinical scores (IKDC, KOOS, VAS for pain, Tegner) showed significant improvements compared to preoperative baseline and a maintenance or even additional improvement compared to the results at 2-years follow-up (Fig. 2a–c). Complete clinical data are given in Table 2. Despite the good-to-excellent clinical results in the group of successful repairs, magnetic resonance imaging showed a deterioration of the MOCART score after the 2-year follow-up from a mean score of 71 to a mean MOCART score of 37 at the final 5-year follow-up (Fig. 2d). While still no signs of inflammation or synovitis were perceived, a significant reduction in the subscores "defect filling", "integration to border zone" and "surface of the repair tissue" was evident. Additionally, a bone bruise reappeared in three patients.

Table 1 Overview of patient cohort; comparison of failed and successful repairs

Group	Successful repair	Failure	*P* value
N	18	5	
Sex	13 male/6 female	3 male/2 female	
Age	35.6 years ± 8.3	31.3 years ± 5.0	n.s
BMI	27.8 kg/m^2 ± 3.5	26.3 kg/m^2 ± 3.1	n.s
Defect size	3.2 cm^2 ± 2.1	4.0 cm^2 ± 1.1	n.s
Defect localisation			
Med. condyle	9	4	
Lat. condyle	3	0	
Patella	4	1	
Trochlea	2	0	

Data given as mean ± standard deviation

In case of clinical failure and reoperation, biopsies were taken from the former lesion/the repair tissue. Two additional biopsies could be taken as two patients of the study collective were re-operated for non-cartilage-related injuries (one patient suffered an ACL injury and another suffered a lateral meniscal tear both necessitating surgery).

Histological evaluation of the failed repairs showed articular cartilage-like tissue without signs of inflammation,

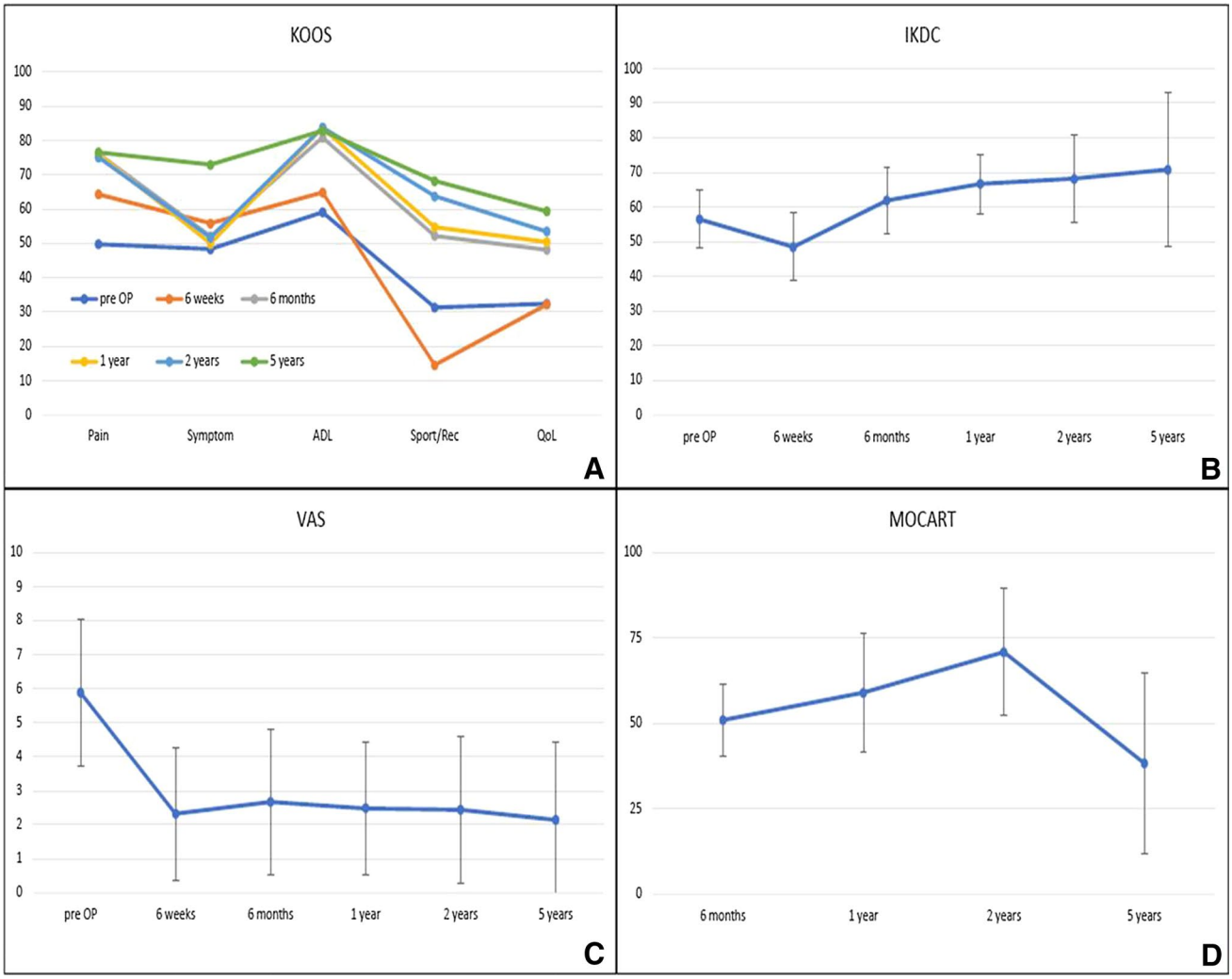

Fig. 2 Overview of clinical and MRI scores. **a** Knee Injury and Osteoarthritis Outcome Score (KOOS). **b** International Knee Documentation Committee Subjective Knee Form (IKDC). **c** Visual analogue scale for pain (VAS). **d** Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score data given as mean and standard deviation

vascularisation or cell death within the former scaffolds (Fig. 3a). Two specimens (one of each group) could not be assessed regarding basal integration, tidemark formation and subchondral bone as insufficient subchondral bone material was taken. Cellular morphology showed vital chondrocytes within all slices but clustering of chondrocytes to a varying degree in all specimens (Fig. 3b). Scoring of the specimen according to the ICRS II criteria showed a mean score of 67 over all subscores within the failure group. The mean VAS rating of the "overall" category was 49 in the failure group. No important histological differences could be perceived between groups apart from a tendency towards better surface architecture in the successful repairs (Fig. 3c). Immunohistochemistry for collagen type I was negative in all but one specimen, which showed a slight positive reaction at the basal layer indicating an overall successful colonization and transformation of the former collagen type I scaffold. Collagen type II was present in all specimens, adding to the articular cartilage-like appearance (Fig. 4a, b).

Discussion

The most important finding of the present study is that the collagen type I scaffold used in this prospective cohort study of large cartilage defects showed clinical failure resulting in revision surgery in 18% of cases 5 years after surgery. Although the remaining patients maintained good clinical results with significant improvements from baseline, the magnetic resonance imaging (MRI) of the repair tissue showed a deterioration over time starting 2 years after implantation.

Table 2 Complete summary of clinical results

	Preoperative	6 weeks	*P* (pre-OP vs. 6 we.)	6 months	*p* (pre-OP vs. 6 mo.)	12 months	*P* (pre-OP vs. 12 mo.)	2 years	*P* (pre-OP vs. 24 mo.)	5 years	*P* (pre-OP vs. 60 mo.)
IKDC	56.53 ± 8.44	48.52 ± 9.82	0.0119	61.98 ± 9.60	0.0061	66.75 ± 8.55	< 0.0001	68.18 ± 12.48	< 0.0001	70.86 ± 22.32	< 0.0001
KOOS											
Pain	49.79 ± 16.33	64.33 ± 19.64	0.0078	76.13 ± 13.26	< 0.0001	76.03 ± 16.79	< 0.0001	75.11 ± 19.91	< 0.0001	76.59 ± 25.28	< 0.0001
Symptom	48.35 ± 10.70	55.86 ± 13.36	0.0131	52.12 ± 11.39	n.s	50.00 ± 12.69	n.s	51.71 ± 15.40	n.s	72.96 ± 25.01	< 0.0001
ADL	59.11 ± 19.67	64.88 ± 20.46	n.s	80.88 ± 11.38	< 0.0001	83.66 ± 13.54	< 0.0001	83.82 ± 16.66	< 0.0001	82.88 ± 21.49	< 0.0001
Sport/Rec	31.35 ± 19.21	14.60 ± 20.20	0.0075	52.22 ± 24.74	0.0063	54.81 ± 22.72	0.0017	63.80 ± 29.13	< 0.0001	68.21 ± 26.57	< 0.0001
QoL	32.45 ± 11.86	32.25 ± 18.64	n.s	48.15 ± 21.29	0.0046	50.46 ± 23.19	0.0038	53.50 ± 24.74	0.0007	59.38 ± 30.00	< 0.0001
VAS	5.88 ± 2.15	2.32 ± 1.95	< 0.0001	2.67 ± 2.15	< 0.0001	2.48 ± 1.95	< 0.0001	2.44 ± 2.15	< 0.0001	2.14 ± 2.28	< 0.0001
Tegner	2.0 (0–4)	2.0 (1–3)	n.s	3.0 (2–10)	< 0.0001	4.0 (2–9)	< 0.0001	4.0 (2–9)	< 0.0001	5.0 (2–9)	< 0.0001
Number of patients	*n* = 28	*n* = 28		*n* = 28		*n* = 28		*n* = 28		*n* = 18 (5 lost to fu, 5 failures)	

Data given as mean ± standard deviation

n.s. not significant, *fu* follow-up

To our knowledge, these are the first prospective, mid-term results for this cell-free collagen type I scaffold-based cartilage repair technique in larger articular cartilage defects. Promising short-term follow-up data 2 years after surgery of this patient cohort were published earlier and good-to-excellent clinical and MRI results after treatment of small cartilage defects with the same scaffold are available [15–17]. But the deterioration of the repair tissue on MRI, as well as the significant amount of patients needing reoperation, puts the use of this implant in larger defects into question.

When comparing the results of this collagen type I scaffold with other cartilage repair techniques, the clinical course, as well as the onset of the deterioration on MRI, shows similarities to the microfracture (MFX) procedure. Although MFX is often referred to as the golden standard in cartilage repair, nowadays it should only be seen as the golden standard in small, preferably traumatic lesions, as there is sufficient evidence that the resulting repair tissue is of limited quality resulting in deterioration of clinical and functional results over time.

The durability of the MFX and thus the long-term results are limited by several aspects. While there is evidence for significant functional improvement 2, 5 and even 7 and 11 years after MFX [4, 5], several studies report a deterioration of the clinical outcome starting between 18 and 36 months after surgery [6, 25]. Different studies have identified larger lesions (> 2–2.5 cm^2), higher ager (> 30–40 years), higher activity, as well as localization of the lesion in the patellofemoral joint as predictors for inferior outcome after microfracture [6, 7, 27–30]. For these indications, the ACT is considered the new golden standard [31]. Although there are still only limited data on cell-free procedures such as this collagen type I scaffold, the present study shows a deterioration 24 months after implantation which compares well to the deterioration seen with the MFX in such larger defects [6]. This implies a comparable quality of the repair tissue which seems insufficient to withstand the higher mechanical forces seen in larger cartilage defects. In a recent review, Riboh et al. compared the efficacy of cartilage repair techniques and concluded that the advanced repair techniques such as the MACT resulted in higher quality repair tissue and lower revision rates at mid- and long-term follow-up [32].

But the downside of these advanced repair techniques is the high economic burden. When considering cost-effectiveness, a recent review by Aae et al. concludes that the MFX procedure is superior with regard to cost-effectiveness at 5-year follow-up [11].

The histological as well as immunohistochemical evaluations of the failed repairs as well as two samples of successful repairs showed an overall successful colonization and transformation of the scaffold. No vascularization, abnormal calcification or inflammation was seen in any specimen.

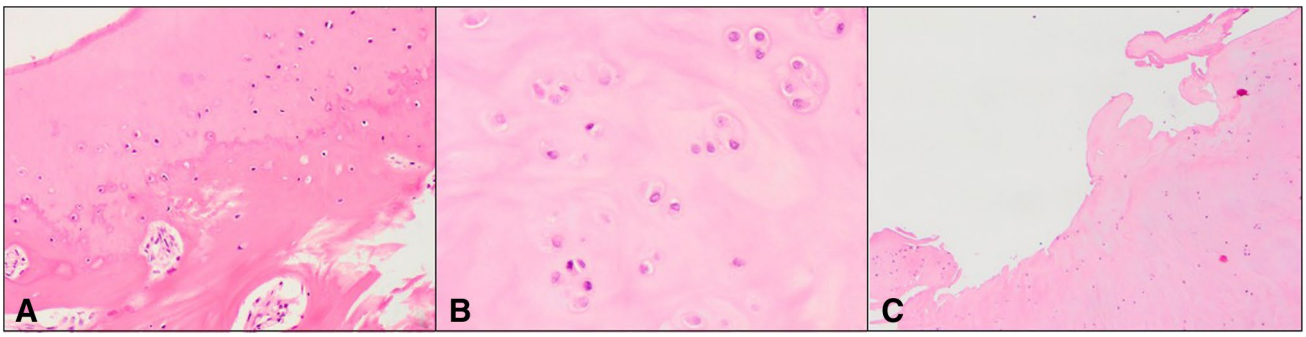

Fig. 3 Hematoxylin–eosin staining of failed repairs. **a** Cartilage-like tissue with intact basal integration (10× magnification). **b** Chondrocyte clustering (20× magnification). **c** Inferior surface architecture (4× magnification)

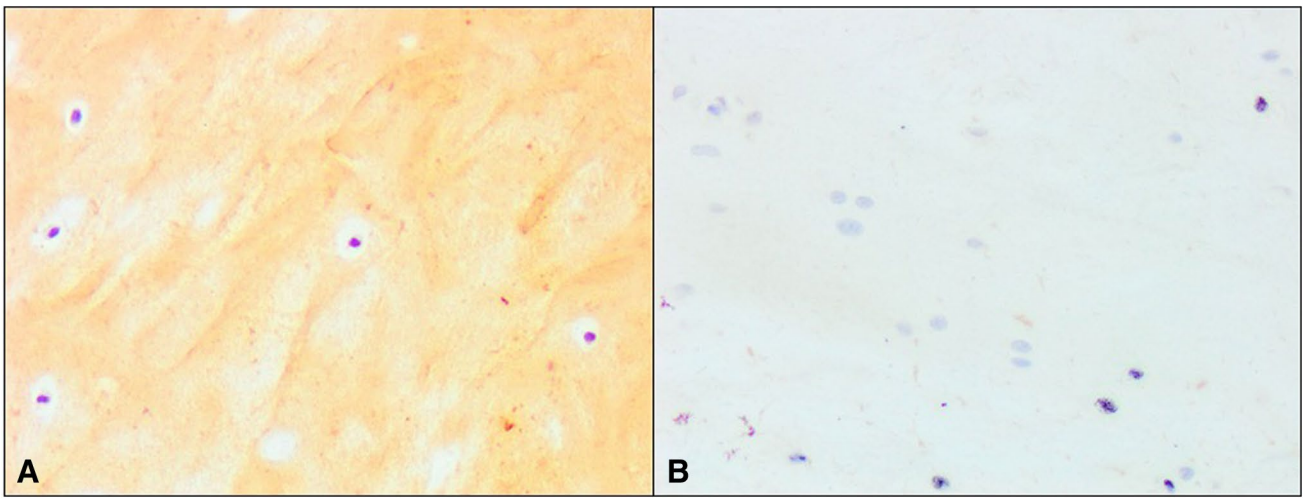

Fig. 4 Immunohistochemistry of a successful repair. **a** Staining for collagen type II. **b** Staining for collagen type I

This, as well as the presence of vital chondrocytes, underlines the results of Schüttler et al. [33] who reported comparable results in a single-patient case report.

But several subscores indicate an inferior tissue quality as, for example, the clustering of chondrocytes, inferior tissue morphology and reduced scoring for matrix staining. The ICRS II Score used in the present study is, despite good reproducibility and validation, still under investigation regarding the correlation between the histological score and the clinical results as well as the weighting of the different subscores [24]. Although the number of specimen is small, the histological assessment is in line with the clinical course, both indicating that the quality of the repair tissue is not sufficient to withstand the mechanical forces in these larger defects.

Another important aspect when comparing microfracture and the collagen scaffold is the potential risk of subchondral bone pathologies such cysts, edema or bone overgrowth or the formation of intralesional osteophytes after microfracture. In a recently published MRI-based study, Mithoefer et al. [8] found intralesional osteophytes in 46.4% of patients 12 months after microfracture, increasing to 62% of patients 22 months after surgery. Although the authors found no significant differences regarding the KOOS Score at 22 months between patients with and without subchondral bone overgrowth, 93% of patients who went on to clinical failure at a mean time of 30.3 ± 17.9 months showed bony overgrowth [8].

The MRI in the present study showed subchondral bone edema in cases of failing repair tissue, which was interpreted as a sign of mechanical overload of the subchondral bone. No subchondral bone overgrowth was seen, except in one patient with an osteochondral lesion necessitating bone grafting prior to implantation of the scaffold. Additionally, even in case of clinical failure and revision surgery, no signs of abnormal calcification were found in the histologic specimen. This advantage of the scaffold over the MFX procedure is most likely due to

the implantation technique, which avoids damage to the subchondral lamina.

In general, autologous chondrocyte transplantation (ACT) is increasingly advocated for defects larger than 2.0–2.5 cm^2 [31]. There are currently several high-quality studies evaluating clinical an radiographical (MRI) results after matrix-induced autologous chondrocyte transplantation (MACT) at 5-year follow-up allowing comparison with the results of this cell-free technique [34, 35].

Ebert et al. [35] compared two different rehabilitation protocols after matrix-induced autologous chondrocyte implantation and reported clinical and MRI results. The reported clinical results (KOOS) for both groups showed significant improvements from preoperative baseline in all subscores (KOOS SR 26.1–67.1; KOOS QOL 33.4–62.6; KOOS Pain 68.9–85.8; KOOS Sympt. 71.6–85.0; KOOS ADL 80.1–92.8) which are comparable to the improvements seen in the present study (see Table 2). With respect to radiological appearance of the repair tissue the authors used a scoring system based on comparable subscores as the MOCART score but rated them from 1 (poor) to 4 (excellent) which makes comparison to our data difficult. Additionally, the authors report a low failure rate of 7.9% at a comparable mean defect size of 3.3 cm^2 [35].

Brix et al. [34] reported results of 53 patients after MACT with a mean follow-up of 9 years ranging from 5 to 12 years but included complex and salvage cases within their study. Overall failure rate was thus 22.6% in this long-term follow-up but occurred at a mean of 2.99 years after surgery. At 5-year follow-up, the subjective IKDC score was 60.5 compared to the 70.9 in the surviving implants in the present study [34].

A limitation of the present study is the lack of a direct control group as comparison with the literature is always under the risk of bias. Additionally, the amount of histologic specimen is small and even smaller in case of successful repair which limits further insight as to why the implants fail.

Conclusion

The use of this cell-free collagen type I scaffold for large cartilage defects of the knee showed increased wear of the repair tissue and clinical failure in 18% of cases at 5-year follow-up. Main reason for failure is most likely the quality of the repair tissue as shown by histological and MRI assessments. Despite the technical advantages of this collagen scaffold compared to alternative procedures such as the ACT and the chance to improve clinical symptoms, patients should be carefully advised regarding the risk of failure between 2 and 5 years after surgery.

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Compliance with ethical standards

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

Informed consent Informed consent was obtained from all individual participants included in the study.

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