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CARTILAGE

Clinical evaluation after matrix-associated autologous chondrocyte transplantation

A COMPARISON OF FOUR DIFFERENT GRAFT TYPES

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Aims

The aim of this retrospective study was to determine if there are differences in short-term clinical outcomes among four different types of matrix-associated autologous chondrocyte transplantation (MACT).

Methods

A total of 88 patients (mean age 34 years (SD 10.03), mean BMI 25 kg/m² (SD 3.51)) with full-thickness chondral lesions of the tibiofemoral joint who underwent MACT were included in this study. Clinical examinations were performed preoperatively and 24 months after transplantation. Clinical outcomes were evaluated using the International Knee Documentation Committee (IKDC) Subjective Knee Form, the Brittberg score, the Tegner Activity Scale, and the visual analogue scale (VAS) for pain. The Kruskal-Wallis test by ranks was used to compare the clinical scores of the different transplant types.

Results

The mean defect size of the tibiofemoral joint compartment was 4.28 cm² (SD 1.70). In total, 11 patients (12.6%) underwent transplantation with Chondro-Gide (matrix-associated autologous chondrocyte implantation (MACI)), 40 patients (46.0%) with Hyalograft C (HYAFF), 21 patients (24.1%) with Cartilage Regeneration System (CaReS), and 15 patients (17.2%) with NOVOCART 3D. The mean IKDC Subjective Knee Form score improved from 35.71 (SD 6.44) preoperatively to 75.26 (SD 18.36) after 24 months postoperatively in the Hyalograft group, from 35.94 (SD 10.29) to 71.57 (SD 16.31) in the Chondro-Gide (MACI) group, from 37.06 (SD 5.42) to 71.49 (SD 6.76) in the NOVOCART 3D group, and from 45.05 (SD 15.83) to 70.33 (SD 19.65) in the CaReS group. Similar improvements were observed in the VAS and Brittberg scores.

Conclusion

Two years postoperatively, there were no significant differences in terms of outcomes. Our data demonstrated that MACT, regardless of the implants used, resulted in good clinical improvement two years after transplantation for localized tibiofemoral defects.

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Article focus

- First study investigating differences in short-term clinical outcomes among four different types of matrix-associated autologous chondrocyte transplantation (MACT).
- Traumatic chondral defects restricted to the tibiofemoral joint.

Key messages

- No significant differences were recorded.
- There was good clinical improvement two years after transplantation.

Strengths and limitations

- This is the first time more than two different matrices have been compared in a clinical trial, as the current literature consists only of small case series or comparisons to microfractures, which do not address the question of whether the matrices available for MACT show differences in terms of patient-reported outcome scores.
- The main advantage of this case control study is the rapid provision of results.
- A limitation of this study is the short-term clinical outcomes of two years. Results over a longer period of time would provide even better data related to the clinical outcome.
- This type of study is prone to bias compared to cohort studies, and its retrospective design allows no presentation of additional data.

Introduction

Articular cartilage lesions are one of the most frequent types of injuries encountered in orthopaedic practice;[1] they show no spontaneous healing response,[2] and often lead to unicompartmental osteoarthritis (OA),[3] which is a common problem among young and active people. Focal defects to the cartilage lead to progredient cartilage self-destruction and joint pain, ultimately resulting in secondary OA.[4]

In the literature, a wide variety of surgical techniques have been described for the treatment of singular defects, for example microfracture (MFX),[5] osteochondral transplantation (OCT),[6] and autologous chondrocyte transplantation (ACT).[7] The common aim of all these techniques is full cartilage regeneration or at least partial recovery of cartilage tissue and, therefore, the ability to return to preoperative activity levels.

Because of improvements and developments in cartilage repair, autologous chondrocyte transplantation (ACT) has become popular.[8,9] Although these techniques require advanced surgical skills and experience, they result in good clinical and radiological outcomes.[10-15] The most common techniques are the third-generation matrix-associated autologous chondrocyte transplantation (MACT) procedures, with a two-step surgical approach. A 3D biocompatible scaffold is used as a carrier for cell growth and seeded with chondrocytes from an initial arthroscopy and is implanted by mini-arthrotomy.[8,9] Biological matrices are composed of cartilage extracellular matrix molecules or biopolymers that function as a scaffold for transplanted chondrocytes to form more hyaline-like repair tissue in articular cartilage defects. The matrices trap the cells in the chondral defect and provide cell-matrix interactions that are designed to stimulate differentiation into articular chondrocytes and production of a hyaline-like extracellular matrix.[4]

As a result of technological advances, MACT - compared to bone marrow-stimulating techniques such as MFX - provides the possibility of differentiation of the cartilage repair tissue, and thus the reformation of hyaline or hyaline-like cartilage.[16,17] It has also been shown that MACT consistently improved patient-reported functional outcomes compared with microfracture.[11,12,18] The safety and clinical effectiveness of this procedure for the treatment of large, symptomatic, full-thickness articular cartilage defects has been demonstrated in several studies, which showed significant improvement in pain, function, and activity up to at least five years.[10,11] However, comparisons between different types of MACT grafts are lacking in the literature. The four most common types are Hyalograft C autografts (Fidia Advanced Biomaterials, Italy), matrix-associated autologous chondrocyte implantation (MACI) (Genzyme, USA), Cartilage Regeneration System (CaReS) (Arthro Kinetics Biotechnology GmbH, Austria), and NOVOCART 3D (TETEC, Germany).

Hyalograft C is a hyaluronan web seeded with previously obtained cells and cultivated in 2D for at least two weeks. MACI is a collagen type I/III membrane seeded with chondrocytes and cultivated in 3D for one week. CaReS is a collagen type I gel; the obtained cells are mixed with the gel directly without monolayer cultivation and then 3D cultivation is performed for three weeks. NOVOCART 3D is a bilayered collagen type I sponge containing chondroitin-sulfate. The cells are isolated from full-depth cartilage cylinders, multiplied in monolayer, and seeded onto the scaffold. This construct is cultivated for two days under 3D condition.[19]

For the first time, this study aims to compare four commonly used transplant types in terms of their clinical outcomes. The hypothesis of this study was that there is a difference in the clinical outcome in regard to the used implant.

Methods

Data collection. In this retrospective cohort study, 101 patients with symptomatic traumatic defects of the articular cartilage of the knee (tibiofemoral joint area), treated between January 2000 and July 2014 with MACT at a single academic clinical centre, were included. Data were extracted from our clinic's cartilage database. During this time period, four different types of MACT grafts were used. First, there were Hyalograft C autografts, which are hyaluronan webs. Second, there was MACI, a collagen type I/III membrane. This collagen membrane is manufactured by Geistlich (Switzerland) and is separately available under the trade name Chondro-Gide. Genzyme uses this membrane to produce their chondrocyte transplant MACI in a production facility in Europe. Third and fourth are the collagen type I gel CaReS and NOVOCART 3D, which is a bilayered collagen type I sponge containing chondroitin-sulfate, respectively. Because differences in clinical outcomes have been described between cartilage transplantations in the tibiofemoral and patellofemoral joint area,[13] only patients with defects restricted to the tibiofemoral joint area were selected for the study.

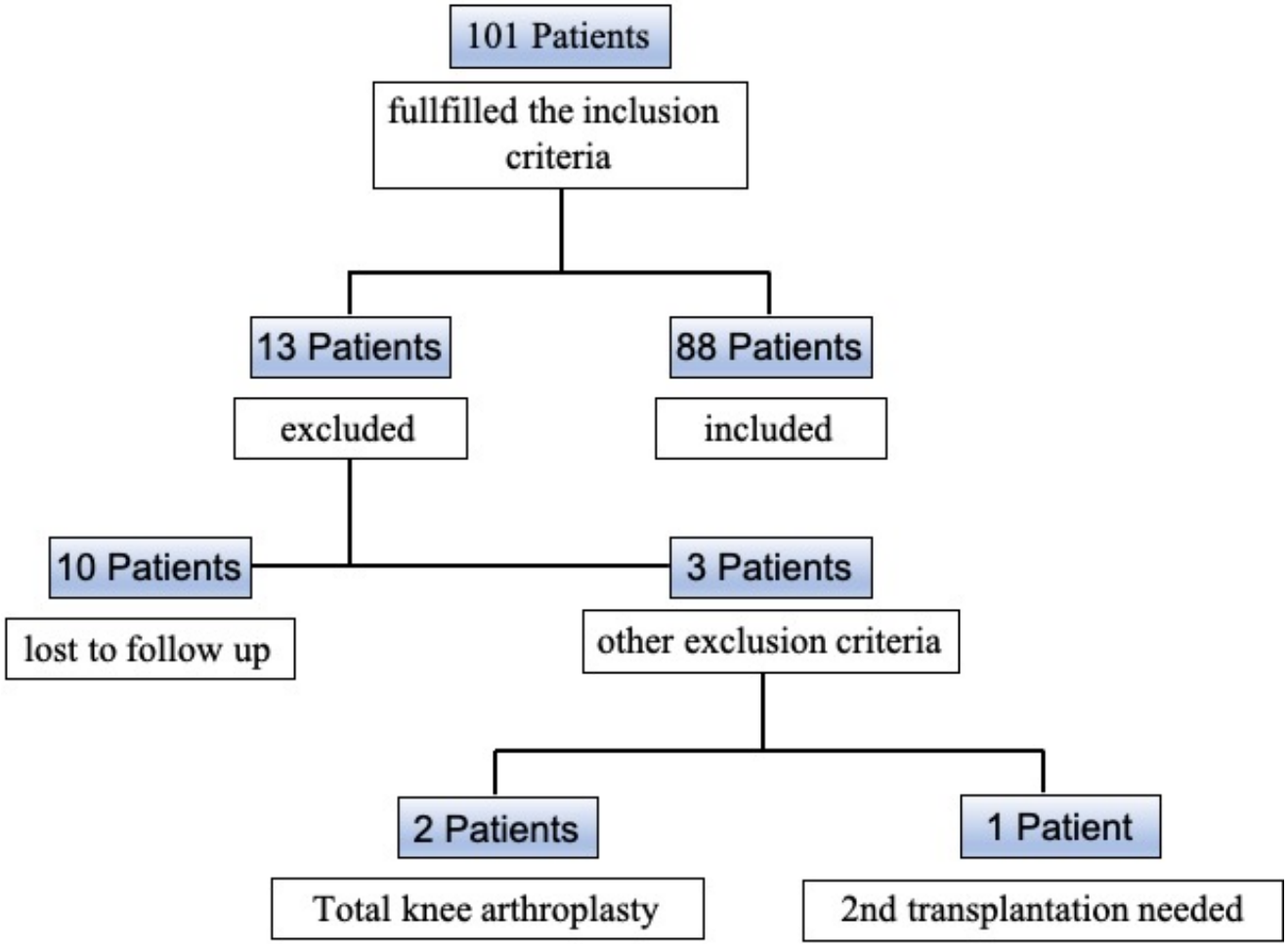

Fig. 1

Patient inclusion flowchart.

Study participants were between 19 and 50 years of age with a defect size of > 2 cm^2 and no knee instability or misalignment (axis deviation > 5°). MRI was performed in all patients to evaluate cartilage defect size and comorbidities, such as ligament rupture or meniscal tears. Additionally, knee stability was tested clinically in each patient prior to surgical intervention. For the anterior cruciate ligament, Lachman's test and anterior drawer were used, as well as pivot shift in the operating theatre. The posterior cruciate ligament was tested with the posterior drawer and stability of the collateral ligaments was tested by stress test in 0° and 30° of knee flexion. There were no restrictions on the upper limit of the defect size or the number of defects. Patients were excluded from the study if they had a BMI of > 30 kg/m^2, totally or partially resected menisci, severe neurological disorders, metabolic arthritis, joint infections, tumours, psychiatric diseases, arthrofibrosis, autoimmune diseases, or if they were pregnant. All patients provided written informed consent before study enrolment. Clinical examinations and evaluations were performed preoperatively and after three, six, and 12 months, whereas the statistical evaluation was performed preoperatively and 24 months after transplantation. Clinical outcomes were evaluated using the International Knee Documentation Committee (IKDC) Subjective Knee Form,[20] the Brittberg score,[21] the Tegner Activity Scale (TAS),[22] and the visual analogue scale (VAS) for pain.[23] After applying the inclusion/exclusion criteria and excluding the patients who were lost to follow-up, 88 patients could be included. Detailed information is presented in Figure 1.

Before the study was started, the corresponding ethical review board of Medical University of Vienna approved the study. The paper was written according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[24] guidelines.

Statistical analysis. The statistical analysis included a tabular description of the demographic data and clinical scores (IKDC Subjective Knee Form, Brittberg score, TAS, and VAS). The statistical evaluation was performed using SPSS software version 23.0 (IBM, USA). Values are presented as the mean and standard deviation (SD). Groups were compared using one-way analysis of variance (ANOVA), followed by post hoc pairwise comparisons to

Table I. Descriptive statistics.

Characteristic	Total	MACI	HYAFF	CaReS	NOVOCART 3D	p-value
Number	88	11	40	21	16	N/A
Sex, n (%)						0.396*
Male	61	10	27	13	11	
Female	27	1	13	8	5	
Mean age, yrs (SD)	34 (10)	33 (6)	36 (10)	31 (10)	34 (9)	0.343†
Mean BMI, kg/m² (SD)	25.2 (3.5)	27.1 (3.0)	24.2 (3.8)	24.6 (4.3)	24.8 (3.2)	0.247†
Mean defect size, cm² (SD)	4.3 (1.7)	3.4 (1.7)‡§	3.9 (1.6)‡	5.1 (1.4)§	4.8 (1.8)	0.021¶
Defect location, n						0.023
MFC	64	8	32	14	10	
LFC	21	3	5	7	6	
MFC + LFC	3	0	3	0	0	

*Chi-squared test.
†Analysis of variance.
‡Statistically significant difference between MACI and CaReS grafts.
§Statistically significant difference between HYAFF and CaReS grafts.
¶Analysis of variance with pairwise comparison using Benjamini-Hochberg correction for multiple comparisons.
CaReS, Cartilage Regeneration System; HYAFF, Hyalograft C; LFC, lateral femoral condyle; MACI, matrix-associated autologous chondrocyte implantation; MFC, medial femoral condyle; N/A, not applicable; SD, standard deviation.

Table II. Clinical data.

Mean score (SD)	Total	MACI	HYAFF	CaReS	NOVOCART 3D
Brittberg, pre-surgical	3.2 (0.6)	3.3 (0.5)	3.1 (0.7)	3.2 (0.6)	3.6 (0.6)
Brittberg, 24 mths post-surgical	2 (0.8)	1.9 (0.7)	2 (0.8)	2.3 (0.7)	2 (0.7)
IKDC pre-surgical	38.3 (10.9)	36 (10.3)	35.7 (6.5)	45.1 (15.8)	37.1 (5.4)
IKDC 24 mths post-surgical	73 (17.5)	71.6 (16.3)	75.3 (18.4)	70.3 (19.7)	71.5 (6.8)
VAS pre-surgical	5.6 (2.0)	6.6 (0.9)	5.5 (2.0)	5.2 (2.5)	5.0 (1.4)
VAS 24 mths post-surgical	2.0 (1.9)	1.8 (1.3)	1.6 (1.7)	2.9 (2.5)	1.6 (0.9)
Tegner-Lysholm pre-surgical	1.9 (1.5)	1.9 (0.7)	1.6 (1.3)	2.5 (2.2)	1.0 (0.8)
Tegner-Lysholm 24 mths post-surgical	4.3 (1.2)	4.3 (1.6)	4.4 (1.3)	4.2 (0.8)	4.2 (1.1)

CaReS, Cartilage Regeneration System; HYAFF, Hyalograft C; IKDC, International Knee Documentation Committee Subjective Knee Form; MACI, matrix-associated autologous chondrocyte implantation; SD, standard deviation; VAS, visual analogue scale for pain.

compare the mean values of each group. To adjust for multiple comparison Benjamini-Hochberg correction was used. Since the data were not normally distributed (Shapiro-Wilk test), non-parametric tests were performed. The Kruskal-Wallis test by ranks was applied to compare the clinical scores of the different transplant types. Statistical tests were considered statistically significant when p-values were lower than 0.05.

Results

A total of 88 MACT procedures were performed in 88 patients (26 female and 62 male) with a mean tibiofemoral lesion size of 4.27 cm² (SD 1.70). The mean age at the time of implantation was 34 years (18 to 48). There were no significant differences found between the four MACT groups regarding age, sex, and BMI (p = 0.343 (ANOVA), 0.396 (chi-squared test), and 0.247 (ANOVA), respectively). However, concerning the defect size, a statistical significance between the MACI and CaReS grafts (p = 0.021 (ANOVA)) as well as between the HYAFF and CaReS grafts (p = 0.023 (ANOVA)) could be detected, with a larger size in the CaReS group. In total, 11 MACI, 40 HYAFF, 21 CaReS, and 16 NOVOCART 3D procedures were performed. The mean BMI and the defect sizes are presented in Table I in detail.

The IKDC Subjective Knee Form score and Tegner activity score increased in all matrices between the pre- and post-surgical evaluations. Furthermore, the overall Brittberg score improved, and pain according to the VAS score showed a solid decrease in all four groups after transplantation. The results are presented in Table II, and in Figures 2 and 3.

The data for the preoperative IKDC Subjective Knee Form score (p = 0.121), as well as for the Tegner Activity Scale (p = 0.296), the Brittberg score (p = 0.429), and the VAS for pain (p = 0.170) showed no statistical significance among the four different transplants. There was also no statistical significance 24 months postoperatively in the IKDC Subjective Knee Form score (p = 0.596), the Tegner Activity Scale (p = 0.717), the Brittberg score (p = 0.203), and the VAS (p = 0.757) among the four different transplants (all p-values calculated using Kruskal-Wallis test).

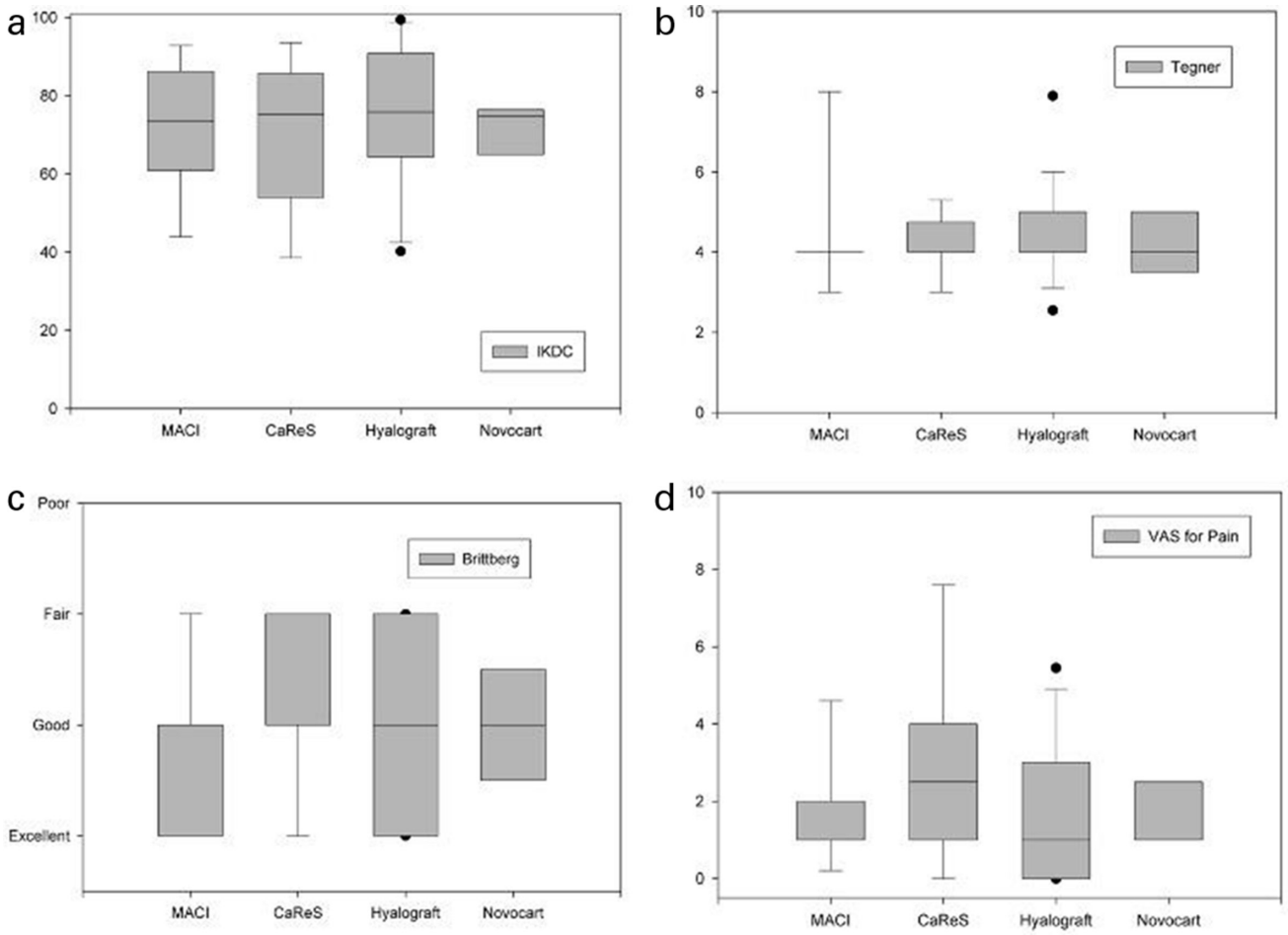

Fig. 2

Box plot showing the clinical results 24 months after matrix-associated autologous chondrocyte transplantation with different scaffolds: a) International Knee Documentation Committee (IKDC) Subjective Knee Form, b) Tegner Activity Scale, c) Brittberg score, and d) visual analogue scale (VAS) for pain. CaReS, Cartilage Regeneration System; MACI, matrix-associated autologous chondrocyte implantation.

These results, as well as the clinical progression of all four matrices after surgery, comparing the pre- and postoperative outcomes, can be seen in Figure 3.

No product-specific adverse events were recorded for any of the 88 patients. Typical postoperative swelling and effusion after the MACT procedure were not rated as product-specific adverse events and resolved in all patients within four to six weeks. To our knowledge, there was no postoperative fever or infection, and no patient had to undergo a reoperation.

Figures 4 to 7 present exemplary MRIs of all used graft types.

Discussion

The basic idea behind autologous chondrocyte implantation is the restoration of a cartilage defect with hyaline cartilage, which provides structural, biomechanical, and biochemical properties necessary to sustain normal joint function and loading in the long term.[25] MACT is an applicable and attractive option for the treatment of cartilage lesions, especially in athletes and active patients. Improvement in clinical outcomes has varied from 70% to 80% in the repair of cartilage in the knee.[26–28] Reduced VAS pain levels and improvements in the Lysholm-Gillquist, Tegner-Lysholm, and International Knee Documentation Classification scale scores ($p < 0.05$) were observed.[26,27] The success of grafts lies in the graft's ability to mimic the native structure and support cell growth and production of a tissue-specific extracellular matrix. MACT requires sufficient expansion of autologous chondrocytes before they are seeded on suitable biodegradable 3D matrices. To meet the requirements for clinical use, a scaffold must be highly biocompatible, non-toxic, and resorbable, and must fulfill specific mechanical properties including stability and resilience.

Despite a wide variety of available scaffolds, only a few are in clinical use for MACT today.[28] Highly different in their manufacturing process as well as in their composition and mechanical properties, these scaffolds are further distinguished as protein-based (e.g. collagen and fibrin),[29,30] polysaccharide-based (e.g. alginate, chitosan, hyaluronic acid, and cellulose),[31–34] and synthetic (e.g.

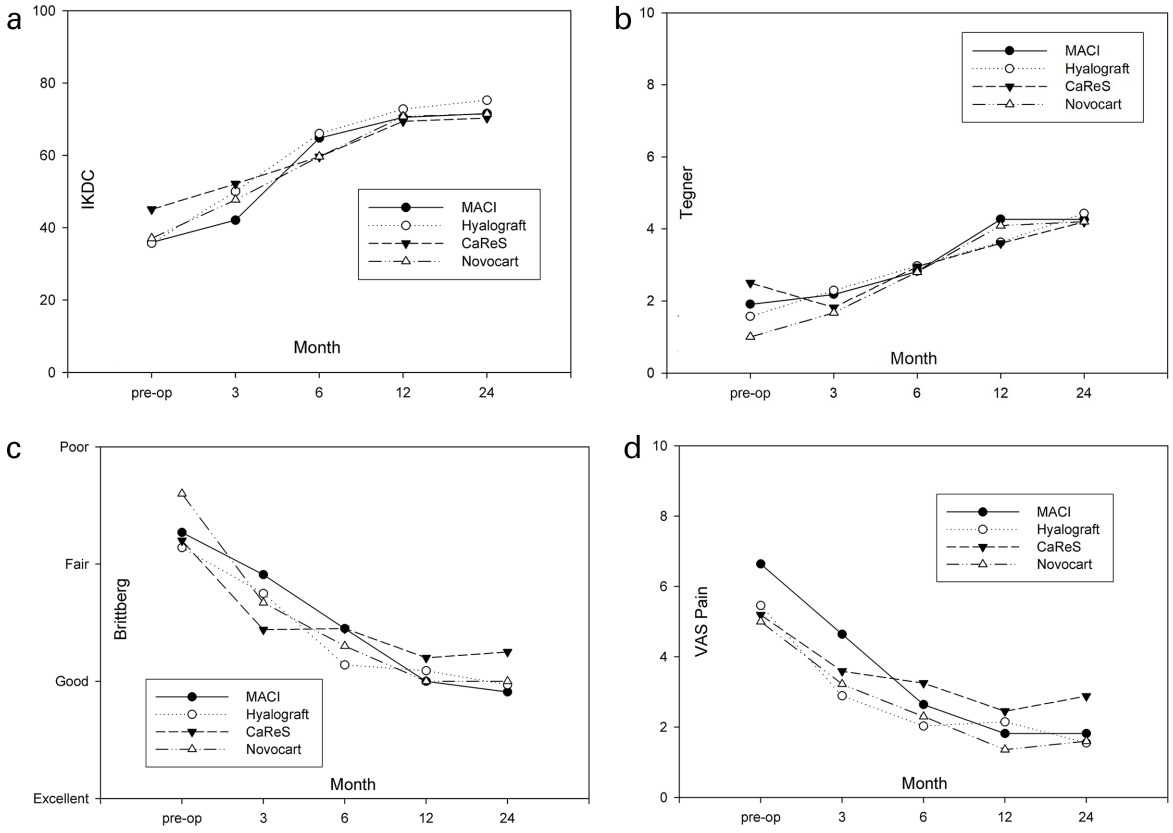

Fig. 3

a) International Knee Documentation Committee (IKDC) Subjective Knee Form, b) Tegner Activity Scale, c) Brittberg, and d) visual analogue scale (VAS) for pain mean scores in patients treated with matrix-associated chondrocyte transplantation with four different matrices over time. CaReS, Cartilage Regeneration System; MACI, matrix-associated autologous chondrocyte implantation.

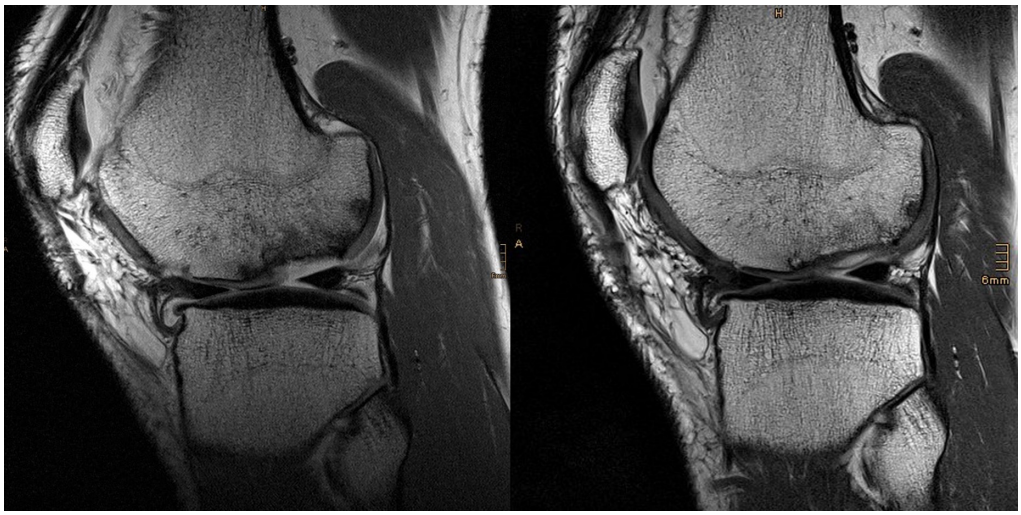

Fig. 4

Preoperative and follow-up MRI of a 45-year-old male patient two years after matrix-associated autologous chondrocyte transplantation procedure with the NOVOCART 3D 543 mm × 270 mm (72 × 72 DPI).

polylactic-coglycolic acid (PGA) and polyethylene glycol (PEG)) biomaterials.[35–37]

Albrecht et al[19] analyzed the influence of scaffold composition and structure on the expression of cartilage-specific genes in these four different clinically applied graft systems. Their data demonstrated that gene expression and cell differentiation differed highly between the analyzed scaffolds at the time of transplantation.

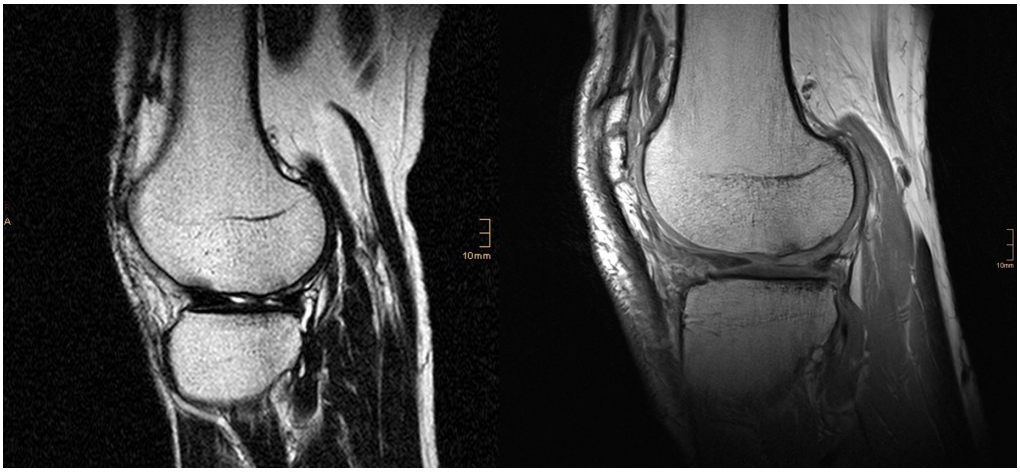

Fig. 5

Preoperative and follow-up MRI of a 31-year-old female patient two years after matrix-associated autologous chondrocyte transplantation procedure with the CaReS-System 588 mm × 268 mm (72 × 72 DPI).

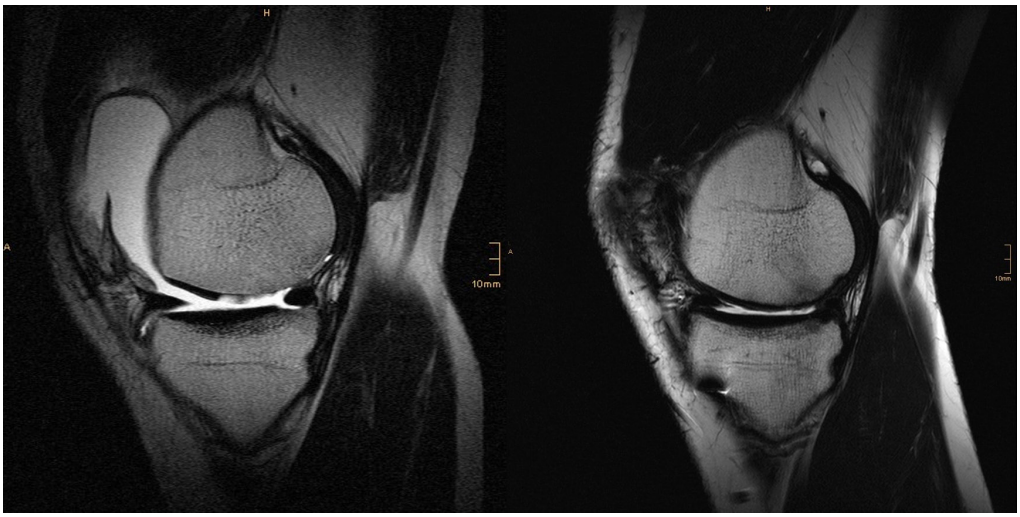

Fig. 6

Preoperative and follow-up MRI of a 25-year-old female patient two years after matrix-associated autologous chondrocyte transplantation procedure with the Hyalograft C Transplantation system.

They suspected these differences resulted from scaffold characteristics as well as culture conditions, e.g. highly variable passage numbers, from the companies. Despite cultivation under 3D conditions, the cell differentiation of all transplant types did not reach the levels of native cartilage.[38] In another recent study, chondrocytic gene expression was correlated with repair tissue quality and graft survival in patients after second-generation autologous chondrocyte implantation (ACI).[39] Despite all the techniques available on the market supporting surgical cartilage restoration, there are several other approaches presented in literature. These approaches are on a cellular level,[40] methods binding on different receptors,[41] or inhibitors on a cellular level,[42] or even acting on T-cells activating anabolic and catabolic genes in articular chondrocytes.[43] However, all these methods are still being explored and have not yet passed the stage of animal or in vitro studies. A promising method seems to be the one presented by Harada et al,[44] where transplantation of autologous bone marrow mesenchymal stem cells with temporary distraction arthroplasty provides the best cartilage repair for a large, chronic osteochondral defect in the weight-bearing area in rabbits.

The novelty of this paper is the comparison of four different graft types among their clinical results in human. Published studies have varied in terms of their quality and which techniques have been compared with one another. To our knowledge, there are no studies comparing more than two different matrices in a clinical trial. The current literature consists only of small case series or comparisons to microfractures,[45] and does not address the question of whether the matrices available for MACT show differences in terms of patient-reported outcome scores. Therefore, this is the first study comparing two-year clinical

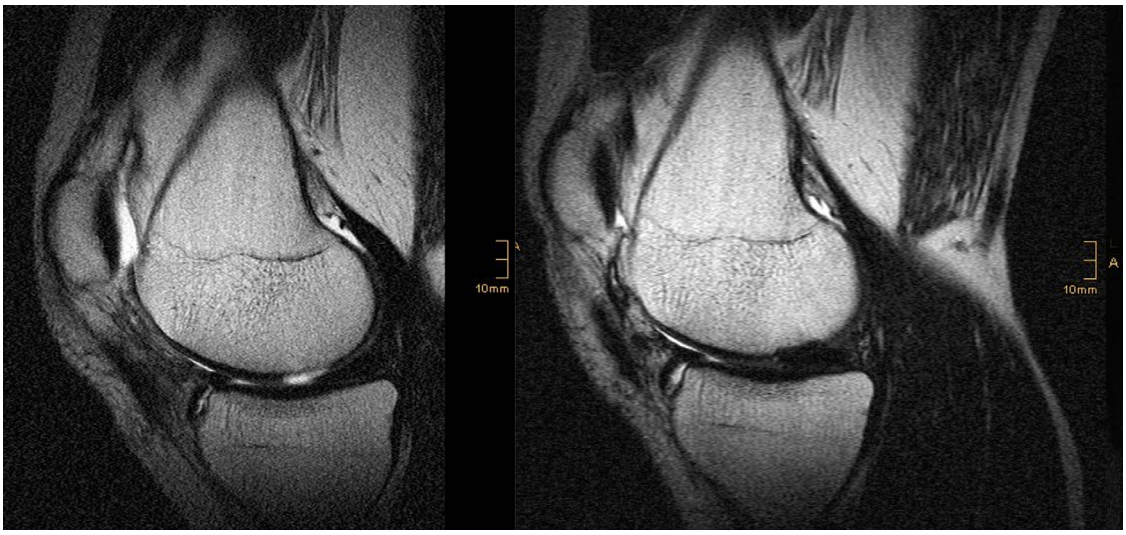

Fig. 7

Preoperative and follow-up MRI of a 35-year-old male patient two years after matrix-associated autologous chondrocyte transplantation procedure with the MACI-System 963 mm × 450 mm (72 × 72 DPI). MACI, matrix-associated autologous chondrocyte implantation.

outcomes of patients treated with different graft types for symptomatic, traumatic chondral defects restricted to the tibiofemoral joint area. Based on clinical score systems, we compared four different graft types to determine differences in short-term clinical outcomes. The major finding of this study was that our data showed no significant differences in the clinical outcomes regarding the graft types used (Table II). As mentioned above, Albrecht et al[19] demonstrated that gene expression and cell differentiation differ highly between the analyzed scaffolds at the time of transplantation. According to our data, this had no major influence on the clinical outcome. Other influencing factors need to be considered, such as the activity level prior to the injury, defect size, age, and rehabilitation. Ebert et al[46] reported statistically significant improvements in clinical scores as well as MRI outcomes five years after MACT. Addressing this particular issue, a controversial influence is the activity level prior to the injury. Mithöefer et al,[14,15] Kreuz et al,[47] and Knutsen et al[17] reported better clinical outcomes for more active patients, whereas Van Assche et al[48] could not find a correlation and attributed this to the different durations of preoperative symptoms. In our study, we showed an enhancement in the above-mentioned scores without going into detail concerning whether there were better clinical outcomes for more active patients. Another influencing factor could be the defect size, which was given no restrictions on the upper limit or number in our study. There are reported differences when comparing single and multiple transplants, with significantly worse results in the group with more than one transplant. This was attributed to the larger defect size and an adapted rehabilitation protocol.[49]

Moreover, age-related differences are mentioned by other authors, demonstrating better results in younger patients, especially with regards to return to sports.[50] As far as this matter is concerned, there was no significant result in our population.

Attention should also be given to rehabilitation after the surgical procedure. The individual patients' progress may deviate, especially in athletes and active patients; therefore, physiotherapeutic support should be adapted and guided by patients' symptoms. A standardized procedure to prevent delamination of the graft is crucial.[18] Further clinical trials and studies, as well as evaluation and comparison of long-term morphological and biomechanical MRI measurements are needed to clarify the influencing parameters.

There are some limitations to this study. Firstly, its retrospective design meant that no additional data can be presented. The aim of the study was to investigate clinical differences between the four used graft types, which can be achieved within the framework of this study design. Another limitation of this study is the relatively low number of patients due to the specific location of defects in the tibiofemoral joint, which was done to obtain a statistically homogeneous group.[13] The additional subdivision of the study population into four groups is another limitation, as is the short follow-up time of only 24 months. The abovementioned small number of patients in the NOVOCART 3D group did not allow for a statistical analysis of the improvement from baseline levels in the IKDC Subjective Knee Form.

In conclusion, our data demonstrated that MACT resulted in good clinical improvement for tibiofemoral defects two years after transplantation, regardless of the graft type used. Different transplant composition and architecture did not significantly influence clinical outcomes in our study population. Further clinical trials comparing a larger number of patients in a randomized prospective study design are needed to clarify clinical outcomes.

References

1. **Curl WW**, **Krome J**, **Gordon ES**, **Rushing J**, **Smith BP**, **Poehling GG**. Cartilage injuries: A review of 31,516 knee arthroscopies. *Arthroscopy*. 1997;13(4):456–460.
2. **Hunziker EB**. Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. *Osteoarthritis Cartilage*. 2002;10(6):432–463.
3. **Schinhan M**, **Gruber M**, **Vavken P**, **et al**. Critical-size defect induces unicompartmental osteoarthritis in a stable ovine knee. *J Orthop Res*. 2012;30(2):214–220.
4. **Schulze-Tanzil G**. Activation and dedifferentiation of chondrocytes: Implications in cartilage injury and repair. *Ann Anat*. 2009;191(4):325–338.
5. **Steadman JR**, **Rodkey WG**, **Rodrigo JJ**. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res*. 2001;391 Suppl:S362: -–S369.
6. **Hangody L**, **Kish G**, **Kárpáti Z**, **Udvarhelyi I**, **Szigeti I**, **Bély M**. Mosaicplasty for the treatment of articular cartilage defects: Application in clinical practice. *Orthopedics*. 1998;21(7):751–756.
7. **Brittberg M**, **Lindahl A**, **Nilsson A**, **Ohlsson C**, **Isaksson O**, **Peterson L**. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889–895.
8. **Brittberg M**. Autologous chondrocyte transplantation. *Clin Orthop Relat Res*. 1999;367:S147–S155.
9. **Marlovits S**, **Zeller P**, **Singer P**, **Resinger C**, **Vécsei V**. Cartilage repair: Generations of autologous chondrocyte transplantation. *Eur J Radiol*. 2006;57(1):24–31.
10. **Behrens P**, **Bitter T**, **Kurz B**, **Russlies M**. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)--5-year follow-up. *Knee*. 2006;13(3):194–202.
11. **Brittberg M**, **Recker D**, **Ilgenfritz J**, **Saris DBF**, **SUMMIT Extension Study Group**. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Five-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2018;46(6):1343–1351.
12. **Jones KJ**, **Kelley BV**, **Arshi A**, **McAllister DR**, **Fabricant PD**. Comparative effectiveness of cartilage repair with respect to the minimal clinically important difference. *Am J Sports Med*. 2019;47(13):3284–3293.
13. **Marlovits S**, **Aldrian S**, **Wondrasch B**, **et al**. Clinical and radiological outcomes 5 years after matrix-induced autologous chondrocyte implantation in patients with symptomatic, traumatic chondral defects. *Am J Sports Med*. 2012;40(10):2273–2280.
14. **Mithöfer K**, **Minas T**, **Peterson L**, **Yeon H**, **Micheli LJ**. Functional outcome of knee articular cartilage repair in adolescent athletes. *Am J Sports Med*. 2005;33(8):1147–1153.
15. **Mithöfer K**, **Peterson L**, **Mandelbaum BR**, **Minas T**. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: Functional outcome and return to competition. *Am J Sports Med*. 2005;33(11):1639–1646.
16. **Bartlett W**, **Skinner JA**, **Gooding CR**, **et al**. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee. *J Bone Joint Surg Br*. 2005;87-B(5):640–645.
17. **Knutsen G**, **Engebretsen L**, **Ludvigsen TC**, **et al**. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am*. 2004;86-A(3):455–464.
18. **Wondrasch B**, **Zak L**, **Welsch GH**, **Marlovits S**. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle on radiographic and clinical outcome after 2 years: a prospective, randomized controlled pilot study. *Am J Sports Med*. 2009;37 Suppl 1:88S-96S.
19. **Albrecht C**, **Tichy B**, **Nürnberger S**, **et al**. Gene expression and cell differentiation in matrix-associated chondrocyte transplantation grafts: A comparative study. *Osteoarthritis Cartilage*. 2011;19(10):1219–1227.
20. **Irrgang JJ**, **Anderson AF**, **Boland AL**, **et al**. Development and validation of the International Knee Documentation Committee subjective knee form. *Am J Sports Med*. 2001;29(5):600–613.
21. **Peterson L**, **Minas T**, **Brittberg M**, **Sjögren-JanssonE**, **Nilsson A**, **Lindahl A**. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res*. 2000;374:212–234.
22. **Tegner Y**, **Lysholm J**. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res*. 1985;(198):43–49.
23. **Boonstra AM**, **Schiphorst Preuper HR**, **Reneman MF**, **Posthumus JB**, **Stewart RE**. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *Int J Rehabil Res*. 2008;31(2):165–169.
24. **Cuschieri S**. The STROBE guidelines. *Saudi J Anaesth*. 2019;13(Suppl 1):S31–S34.
25. **Hangody L**, **Vásárhelyi G**, **Hangody LR**, **et al**. Autologous osteochondral grafting--technique and long-term results. *Injury*. 2008;39(Suppl 1): :32–39.
26. **Brittberg M**. Cell carriers as the next generation of cell therapy for cartilage repair: a review of the matrix-induced autologous chondrocyte implantation procedure. *Am J Sports Med*. 2010;38(6):1259–1271.
27. **Gilbert JE**. Current treatment options for the restoration of articular cartilage. *Am J Knee Surg*. 1998;11(1):42–46.
28. **Niemeyer P**, **Lenz P**, **Kreuz PC**, **et al**. 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*. 2010;26(8):1074–1082.
29. **Cherubino P**, **Grassi FA**, **Bulgheroni P**, **Ronga M**. Autologous chondrocyte implantation using a bilayer collagen membrane: a preliminary report. *J Orthop Surg*. 2003;11(1):10–15.
30. **Steinwachs M**. New technique for cell-seeded collagen-matrix-supported autologous chondrocyte transplantation. *Arthroscopy*. 2009;25(2):208–211.
31. **Hendrickson DA**, **Nixon AJ**, **Grande DA**, **et al**. Chondrocyte-fibrin matrix transplants for resurfacing extensive articular cartilage defects. *J Orthop Res*. 1994;12(4):485–497.
32. **Hoemann CD**, **Sun J**, **McKee MD**, **et al**. Chitosan-glycerol phosphate/blood implants elicit hyaline cartilage repair integrated with porous subchondral bone in microdrilled rabbit defects. *Osteoarthritis Cartilage*. 2007;15(1):78–89.
33. **Pavesio Aet al**. Hyaluronan-based scaffolds (Hyalograft C) in the treatment of knee cartilage defects: preliminary clinical findings. *Novartis Found Symp*. 2003;249: p. 203-17(discussion 229-33):234-8–239-41.
34. **Selmi TAS**, **Verdonk P**, **Chambat P**, **et al**. Autologous chondrocyte implantation in a novel alginate-agarose hydrogel: outcome at two years. *J Bone Joint Surg Br*. 2008;90-B(5):597–604.
35. **Munirah S**, **Kim SH**, **Ruszymah BH**, **Khang G**. The use of fibrin and poly(lactic-co-glycolic acid) hybrid scaffold for articular cartilage tissue engineering: an in vivo analysis. *Eur Cell Mater*. 2008;15: :41–52.
36. **Nicodemus GD**, **Villanueva I**, **Bryant SJ**. Mechanical stimulation of TMJ condylar chondrocytes encapsulated in PEG hydrogels. *J Biomed Mater Res A*. 2007;83(2):323–331.
37. **Vinatier C**, **Magne D**, **Moreau A**, **et al**. Engineering cartilage with human nasal chondrocytes and a silanized hydroxypropyl methylcellulose hydrogel. *J Biomed Mater Res A*. 2007;80(1):66–74.
38. **Vinatier C**, **Mrugala D**, **Jorgensen C**, **Guicheux J**, **Noël D**. Cartilage engineering: a crucial combination of cells, biomaterials and biofactors. *Trends Biotechnol*. 2009;27(5):307–314.
39. **Ackermann J**, **Merkely G**, **Mestriner AB**, **Shah N**, **Gomoll AH**. Increased chondrocytic gene expression is associated with improved repair tissue quality and graft survival in patients after autologous chondrocyte implantation. *Am J Sports Med*. 2019;47(12):2919–2926.
40. **Li H**, **Yang HH**, **Sun ZG**, **Tang HB**, **Min JK**. Whole-transcriptome sequencing of knee joint cartilage from osteoarthritis patients. *Bone Joint Res*. 2019;8(7):290–303.
41. **Zhao X**, **Huang P**, **Li G**, **Lv Z**, **Hu G**, **Xu Q**. Activation of the leptin pathway by high expression of the long form of the leptin receptor (Ob-Rb) accelerates chondrocyte senescence in osteoarthritis. *Bone Joint Res*. 2019;8(9):425–436.
42. **Zhang R-K**, **Li G-W**, **Zeng C**, **et al**. Mechanical stress contributes to osteoarthritis development through the activation of transforming growth factor beta 1 (tgf-β1). *Bone Joint Res*. 2018;7(11):587–594.
43. **Zhang M**, **Lu Q**, **Budden T**, **Wang J**. NFAT1 protects articular cartilage against osteoarthritic degradation by directly regulating transcription of specific anabolic and catabolic genes. *Bone Joint Res*. 2019;8(2):90–100.
44. **Harada Y**, **Nakasa T**, **Mahmoud EE**, **et al**. Combination therapy with intra-articular injection of mesenchymal stem cells and articulated joint distraction for repair of a chronic osteochondral defect in the rabbit. *J Orthop Res*. 2015;33(10):1466–1473.

45. **Wylie JD**, **Hartley MK**, **Kapron AL**, **Aoki SK**, **Maak TG**. What is the effect of matrices on cartilage repair? A systematic review. *Clin Orthop Relat Res*. 2015;473(5):1673–1682.
46. **Ebert JR**, **Robertson WB**, **Woodhouse J**, **et al**. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. *Am J Sports Med*. 2011;39(4):753–763.
47. **Kreuz PC**, **Steinwachs M**, **Erggelet C**, **et al**. Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. *Am J Sports Med*. 2007;35(8):1261–1268.
48. **Van Assche D**, **Van Caspel D**, **Vanlauwe J**, **et al**. Physical activity levels after characterized chondrocyte implantation versus microfracture in the knee and the relationship to objective functional outcome with 2-year follow-up. *Am J Sports Med*. 2009;37 Suppl 1:42–49.
49. **Zak L**, **Aldrian S**, **Wondrasch B**, **Albrecht C**, **Marlovits S**. Ability to return to sports 5 years after matrix-associated autologous chondrocyte transplantation in an average population of active patients. *Am J Sports Med*. 2012;40(12):2815–2821.
50. **Mithoefer K**, **Hambly K**, **Della Villa S**, **Silvers H**, **Mandelbaum BR**. Return to sports participation after articular cartilage repair in the knee: scientific evidence. *Am J Sports Med*. 2009;37(Suppl 1):167–176.

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