Matrix-Associated and Autologous Chondrocyte Transplantation in the Ankle: Clinical and MRI Follow-up after 2 to 11 Years

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Abstract

Background: New matrix-associated autologous chondrocyte transplantation (MACT) techniques may facilitate the treatment of chondral defects in talar cartilage and provide good clinical outcome in the long term. The aim of this prospective case series was to monitor the clinical outcome after autologous chondrocyte transplantation (ACT) and MACT in the ankle to gain data on the mid-term efficacy of the procedure. *Methods:* Seventeen cases of talar cartilage defects were assessed with the American Orthopaedic Foot and Ankle Score (AOFAS), a modified Cincinnati score, and a subjective ankle-hindfoot score (AHS) at a mean of 61 (24-135) months after surgery. Nine patients consented to an additional magnetic resonance imaging (MRI) exam, including T2 mapping at 3T. ACT was carried out with a periosteal flap (4 cases) or with a matrix-assisted ACT technique (Hyalograft C; 13 cases). *Results:* Significant improvement was found in all cases. The AOFAS improved from 50.0 to 87.3, the AHS from 43.8 to 84.1, and the modified Cincinnati score from 2.9 to 6.9. MRI data demonstrated good defect filling, and T2 mapping results indicated that the collagen and water content of the repair tissue was comparable to adjacent cartilage. *Discussion:* MACT and ACT in the ankle can provide good and excellent long-term outcome and resulted in repair tissue with T2 properties similar to native cartilage in the majority of cases. Matrix-assisted implantation with the hyaluronan matrix allows for a less invasive surgical procedure. *Level of evidence*: 4; prospective case series study.

Keywords

Cartilage lesions in the talus frequently result from trauma[1,2]; arthroscopic assessment of 288 consecutive cases with ankle joint fractures revealed that 79.2% had cartilage lesions, and a retrospective magnetic resonance imaging (MRI) analysis of 430 cases of twisted ankles demonstrated that 50% were affected by osteochondral lesions associated with ligament damage.[3] In contrast, approximately 7% to 15% of patients with osteochondral lesions in the talus have no previous history of trauma and mostly relate to osteochondritis dissecans (OCD).[1] The overall frequency of osteochondral lesions in the ankle has undoubtedly been underestimated.[4]

Although defects can often be asymptomatic, continuing overuse, joint instability, and repetitive trauma can establish a chronic symptomatic cartilage defect that may eventually result in osteoarthritis. It is worth noting that no long-term study of untreated osteochondral defects demonstrating progressive deterioration is available at this time.[5]

However, surgical treatment of the defect is essential to relieve pain and has the goal to prevent the onset of osteoarthritis.

Surgical treatment options include refixation or removal of loose fragments, microfracture or drilling of the defect, mosaicplasty, and osteochondral grafting, including allograft implantation in severe cases of osteochondral

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destruction. Satisfactory results are reported in the majority of cases. Excision curettage and bone marrow stimulation are reported to yield an overall success rate of 85% in OCD.[6] In mosaicplasty, good to excellent results are reported in 94%, but instable fixation, incomplete defect fill, and incongruent repair site surface in osteochondral grafting as well as immunological problems in allograft procedures remain inherent limitations of mosaicplasty[7]; furthermore, grafting procedures often require osteotomy of the medial malleolus and an extensive surgical approach, including donor site morbidity in the ipsilateral knee.[7]

Autologous chondrocyte transplantation (ACT) using a sutured periosteal flap over the defect site for providing a compartment for the transplanted cell suspension is a promising technique for the treatment of full-thickness focal chondral defects of the knee.[8-13] The excellent long-term clinical outcomes obtained in the knee[8] encouraged clinicians to use the ACT procedure also to treat chondral and osteochondral defects in the ankle joint. The short- and mid-term clinical and histological outcomes are promising,[14-19] albeit on a limited number of cases.

The ACT procedure in the ankle often requires osteotomy of the medial malleolus[1] to assess the defect and perform the periosteal patching. Furthermore, ACT is associated with intrinsic limitations, such as problems with harvesting and suturing of the periosteum, delamination of the graft, and periosteal hypertrophy.[8,20]

In matrix-associated autologous chondrocyte transplantation (MACT), the periosteal flap is replaced by biodegradable polymers.[21-26] In this series, we used a tissue engineered graft (Hyalograft C; Fidia Advanced Biopolymers, Abano Terme, Italy), composed of autologous cells grown on a biodegradable, hyaluronan-based HYAFF scaffold.[27-32] This engineered cartilage graft allows for a minimum exposure of the joint during the surgical procedure since it can be implanted in mini-invasive arthrotomy or in arthroscopy.[14,31,33]

Aside from defect filling, repair tissue (RT) composition influences clinical long-term outcome, and it is therefore of considerable interest to assess RT composition in the course of the clinical evaluation of cartilage repair techniques.[34,35] Recent progress in MRI technology has yielded imaging techniques to directly visualize molecular tissue properties in cartilage repair.[36,37] Among these, T2 mapping has been demonstrated to provide information on cartilage repair tissue collagen organization and water content.[38,39]

This study reports on the clinical outcome of 17 cases after ACT and after Hyalograft C; 9 patients also consented to MRI follow-up, including T2 mapping at 3T. The study also discusses technical issues of ACT and MACT in the ankle.

Patients and Methods

Patients

Seventeen patients with chronic symptomatic cartilage defects in the ankle (7 men, 10 women; mean age at the time of implantation 28 [19-44] years and mean body mass index 25.3 ± 4.2 [18.6-34.4] kg/m^2) were included. Four cases had traumatic lesions, 12 cases had OCD, and 1 case had a defect resulting from a hemangioma. All lesions were singular and located on the talus (6 lateral, 11 medial). The mean size of the defects was 1.5 ± 0.7 cm^2. The duration of symptoms before surgery was between 2 months and 15 years (mean 4 years). Twelve patients had previous surgery: 6 were treated by microfracture as first-line treatment, and 6 had obtained arthroscopic debridement. During the arthroscopic harvest procedure, loose bodies were found in 6 cases (for details, see **Table 1**).

Biopsy and Defect Assessment

All patients had arthroscopy after clinical and radiological examination and were biopsied for chondrocyte transplantation from the affected ankle joint. The arthroscopy was performed through an anteromedial and anterolateral arthroscopic portal using a standard technique. The joint was inspected and the cartilage defect measured and graded to assess treatment options. Grade 3 and 4 lesions (according to the Outerbridge classification) larger than 1 cm in diameter were included. The biopsy was taken from the anterior aspect of the talus from the non-weightbearing anterior cartilage rim. The cartilage sample size was a minimum of 120 mg; in the 6 cases with loose bodies, intact cartilage was harvested, but the transplants were augmented with cells from the loose bodies.

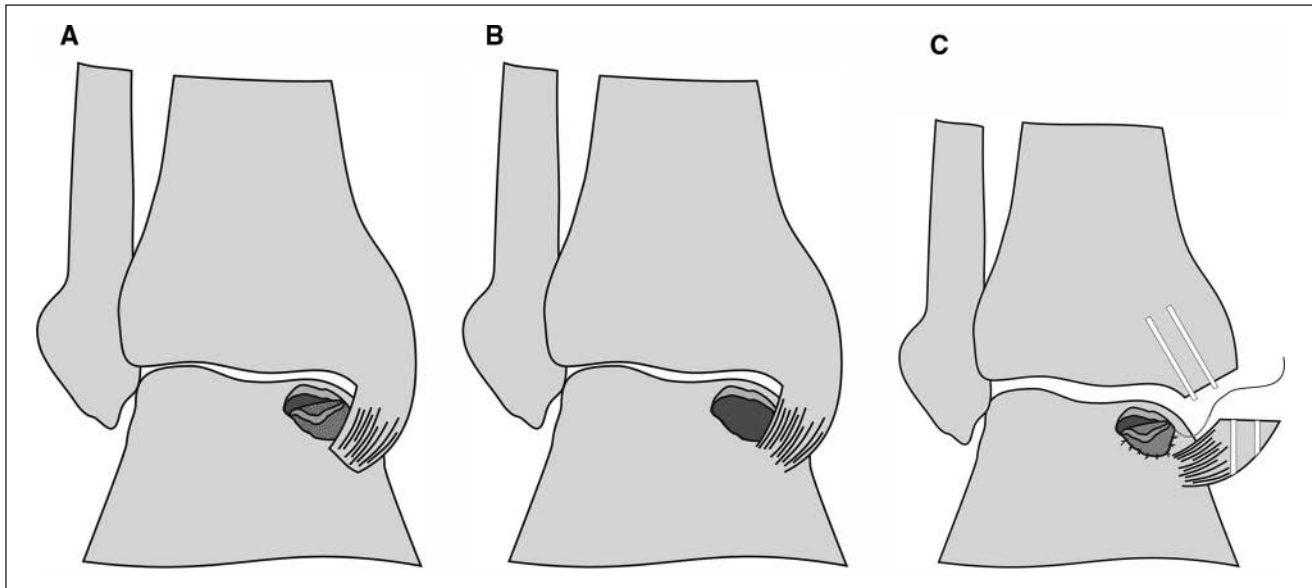### Autologous Chondrocyte Transplantation

Chondrocytes were enzymatically isolated, expanded over a period of at least 3 weeks, and subsequently transplanted as a cell suspension under a patched periosteal flap (Carticel; Genzyme Tissue Repair, Cambridge, MA) as reported in previous studies.[18]

Depending on the defect location, a medial or lateral miniarthrotomy was performed and the defect debrided to achieve a clean osseous ground of the defect with perpendicular borders. The periosteal flap was harvested from the adjacent distal tibia and sutured to the adjacent cartilaginous border with 6-0 Vicryl sutures to create a waterproof compartment in the defect. Finally, the chondrocyte suspension was injected into the defect site underneath the periosteal patch and closed with the last suture (**Fig. 1**). It may be worth noting that osteotomy was inevitable in two

Table I. Parameters for All Patients

Case	Cartilage Repair Type	First-Line Treatment	Age at Implantation	BMI, kg/m²	Defect Size, cm²	Pathology	OBR	Location	Surgery Date	Follow-up Period, mo	Presurgery			Postsurgery		
											AOFAS	AHS	CIN	AOFAS	AHS	CIN
1	ACT	NO	25	18.6	1	Hemangioma	4	Lat	IV./96	135	26	10	3	81	60	4
2	ACT	NO	42	34.4	3	OCD	3	Lat	III./99	100	16	25	0	96	90	6
3	ACT	NO	29	24.9	2	OCD	3	Med	III./99	100	57	45	3	100	100	9
4	ACT	NO	25	21.6	2	OCD	4	Med	V./01	87	28	30	3	87	90	8
5	Hyalograft	MFX	33	27.8	1	Trauma	4	Lat	III./05	38	60	60	2	85	70	4
6	Hyalograft	MFX	30	29.6	0.8	Trauma	4	Lat	IV./02	73	62	45	3	72	50	3
7	Hyalograft	MFX	19	26.3	1.5	OCD	4	Med	I./07	29	61	55	4	75	90	8
8	Hyalograft	NO	19	26.3	1.5	OCD	4	Med	VII./06	35	61	55	4	100	100	8
9	Hyalograft	MFX	30	28.4	1.5	OCD	4	Med	VII./02	70	10	10	1	80	90	8
10	Hyalograft	NO	44	28.3	2	OCD	3	Med	IV./05	27	54	45	3	77	75	7
11	Hyalograft	NO	21	25	2.5	OCD	3	Lat	VI./01	73	39	45	3	88	90	8
12	Hyalograft	MFX	22	18.6	1	OCD	4	Med	III./04	50	34	30	2	85	85	8
13	Hyalograft	NO	23	22.9	2	OCD	4	Med	VI./04	37	86	85	5	100	95	8
14	Hyalograft	MFX	31	24.7	0.8	OCD	4	Med	XII./03	53	70	40	3	90	85	8
15	Hyalograft	NO	32	29.4	1.5	Trauma	4	Med	IX./04	44	60	65	3	90	90	8
16	Hyalograft	NO	33	21.3	0.5	OCD	4	Med	VIII./05	24	68	60	3	88	75	5
17	Hyalograft	NO	19	21.3	1.5	Trauma	4	Lat	I./04	65	58	40	4	90	95	8
Mean			28.1	25.3	1.5					61.2	50.0	43.8	2.9	87.3	84.1	6.9
Standard deviation			7.5	4.2	0.7					31.0	20.8	19.3	1.2	8.6	13.8	1.8
Minimum			19	18.6	0.5					24	10	10	0	72	50	3
Maximum			44	34.4	3					135	86	85	5	100	100	9

ACT = autologous chondrocyte transplantation; AHS = ankle-hindfoot score; AOFAS = American Orthopaedic Foot and Ankle Score; BMI = body mass index; CIN = Cincinnati Rating Scale score; MFX = microfracture; NO = no specific previous cartilage surgery; OBR = outerbridge grade; OCD = osteochondritis dissecans; The roman numerals indicate the month of surgery.

Figure 1. Surgical procedure of autologous chondrocyte transplantation with a periosteal flap: osteochondral defect with a (**A**) delaminated piece of cartilage, (**B**) debrided defect, and (**C**) malleotomy and suturing of the periosteal flap.

cases because of the suturing of the graft rather than because of the accessibility of the defect sites.

MACT with a Hyaluronan Matrix (Hyalograft C)

In 13 patients, the cultured cells were seeded on a hyaluronan matrix (Hyalograft C; Fidia Advanced Biopolymers). Briefly, the graft consists of a hyaluronan-based polymer that promotes cell differentiation and undergoes spontaneous hydrolysis *in vivo*. After 2 weeks of *in vitro* expansion, the chondrocytes are seeded on the scaffold. After another 2 weeks, the graft already has extracellular matrix components and is ready for implantation.[26,28,32,40]

The joint was opened through a medial or lateral mini-arthrotomy. Under moderate traction and plantar flexion, the defect was accessible from the anterior (**Fig. 2**). In 3 of 13 cases, medial malleolar osteotomy was necessary to achieve satisfactory access to the defect site. After debridement of the defect, the matrix was trimmed to fit the defect and implanted with fibrin glue fixation on the borders of the defect. The tourniquet was opened and the joint moved to verify graft stability.

Six cases obtained microfracture as first-line treatment. In those cases, the cartilage sample was frozen with the option to be processed for implantation until up to 12 months after biopsy.

Postoperative Rehabilitation

Postoperatively, the patients received an immobilization plaster for 2 days to avoid early dislodgment of the grafts.

After that, patients with medial malleolar osteotomy received a walker brace to allow early movement out of the brace. Non-weightbearing ambulation was allowed for 6 weeks using crutches, followed by 4 to 6 weeks of gradual weight bearing. Cycling on a stationary cycle was allowed after 6 weeks and more extensive walking after 6 months. Moderate sports such as jogging were started after 9 to 12 months, but stop-and-go activity and impact sports were not recommended until after 18 months.

Clinical Follow-up

Follow-up was carried out 61 ± 31.0 (24-135) months after implantation (from baseline to last follow-up, see **Table 1**). Preoperative and follow-up evaluation was performed with the American Orthopaedic Foot and Ankle Score (AOFAS; Ankle-Hindfoot Scale),[41] a subjective ankle-hindfoot score,[42] and the modified Cincinnati Rating Scale[43] adapted for ankle patients. Statistical analysis was performed with descriptive analysis of means and standard deviation, and double-tailed, paired *t* tests were performed to assess statistical significance.

MRI Follow-up

Nine patients consented to additional MRI examinations at follow-up. All measurements were performed on a 3T MR unit. For morphologic imaging, an isotropic 3-dimensional (3D) Gradient Echo (True FISP) sequence with a $0.4 \times 0.4 \times 0.4$-mm resolution was used for volumetric defect site measurements; a proton density turbo spin echo
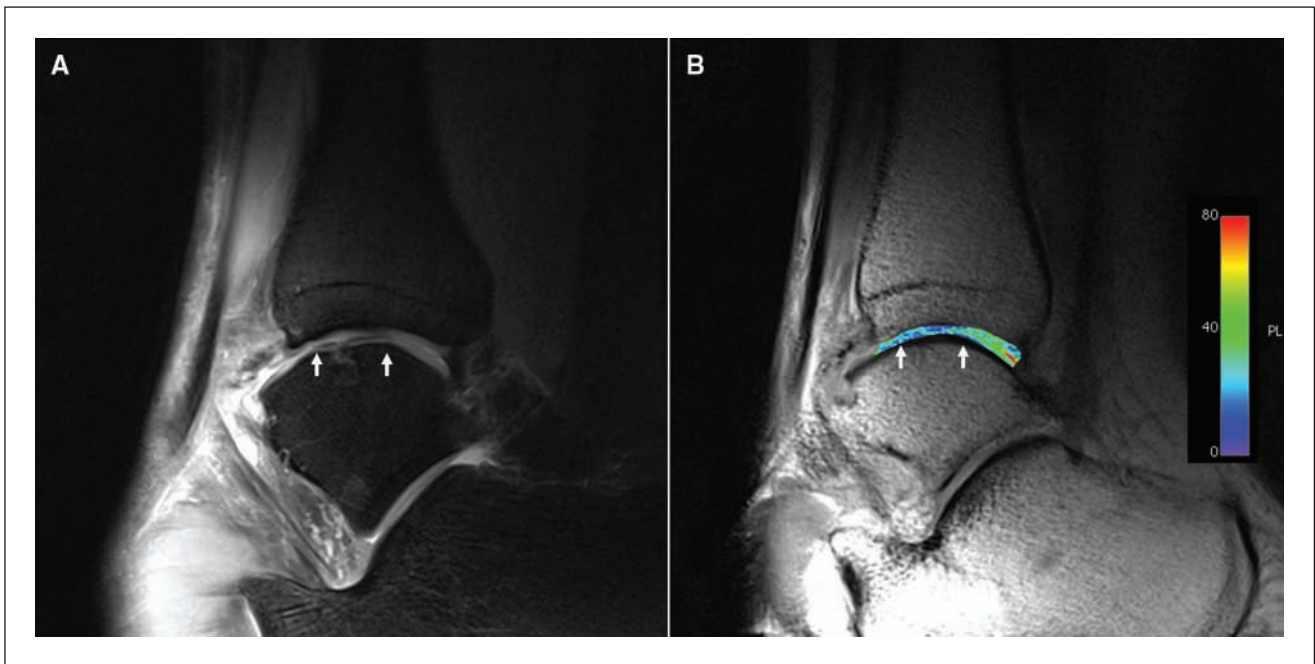
Figure 2. (**A**) Morphologic sagittal proton density-weighted image and (**B**) corresponding T2 map. Subchondral alterations are visible in the area of the repair site (white arrows). A homogeneous distribution of T2 values throughout is found, but values are lower at the repair site.

(PD-FS-TSE) sequence with an in-plane resolution of 0.3 × 0.3 mm was used to assess articular cartilage, effusion, and the subchondral bone. T2 mapping was carried out with a multiecho spin echo sequence that yielded an in-plane resolution of 0.4 × 0.4 mm with a slice thickness of 3 mm; TR was 1.000 s, and 6 different echo times (13.8 ms, 27.6 ms, 41.4 ms, 55.3 ms, 69 ms, and 82.8 ms) were used. T2 maps were calculated with a pixel-wise, monoexponential non-negative least squares (NNLS) fit analysis (MapIt, Siemens, Munich, Germany).

An experienced musculoskeletal radiologist blinded to clinical outcome (S.T., 20 years of experience) assessed the morphologic MRI, considering defect filling volume (<25%, 25%-50%, 50%-75%, 75%-100%, 100%, and >100%), the integrity of the surface (no fissures, fissures <50%, fissures >50%, full-depth fissures), subchondral edema (minor, moderate <2 cm, severe >2 cm), and effusion.

Regarding T2 mapping, region-of-interest (ROI) analysis was carried out by assessing the full thickness of RT and reference cartilage (RC) layers in each slice. The data from all slices were then used to calculate mean RT T2 and RC T2, respectively, and relative T2 (rT2) values were calculated for the individual cases (rT2 = RT T2/RC T2).[44,45]

Results

Clinical Outcome

At the time of inclusion, the preoperative AOFAS was 50.0 ± 20.8 (10-86), the subjective ankle-hindfoot score was 43.8 ± 19.3 (10-85), and the modified Cincinnati Rating Scale score was 2.9 ± 1.2 (0-5). The time period between biopsy and cell implantation was 6 weeks to 6 months in regular cases; in the microfracture first-line treatment cases, the interval between biopsy and implantation was 4 to 12 months.

The follow-up period was a mean of 61 (24-135) months (4 years; range, 2-11 years) with no loss to follow-up. At the time of evaluation, all patients considered ankle joint function improved and could pursue everyday life activities without restrictions. The postoperative AOFAS was 87.3 ± 8.6 (72-100) points, the subjective ankle-hindfoot score was 84.1 ± 13.8 (50-100), and the modified Cincinnati Rating Scale score was 6.9 ± 1.8 (3-9). All clinical scores improved significantly ($P < 0.001$ in paired t tests; see **Fig. 3**).

No complications or major adverse events occurred. All osteotomies healed without complications, and 2 patients opted for screw removal. Two other patients (Hyalograft group) underwent a second-look arthroscopy. In one, a
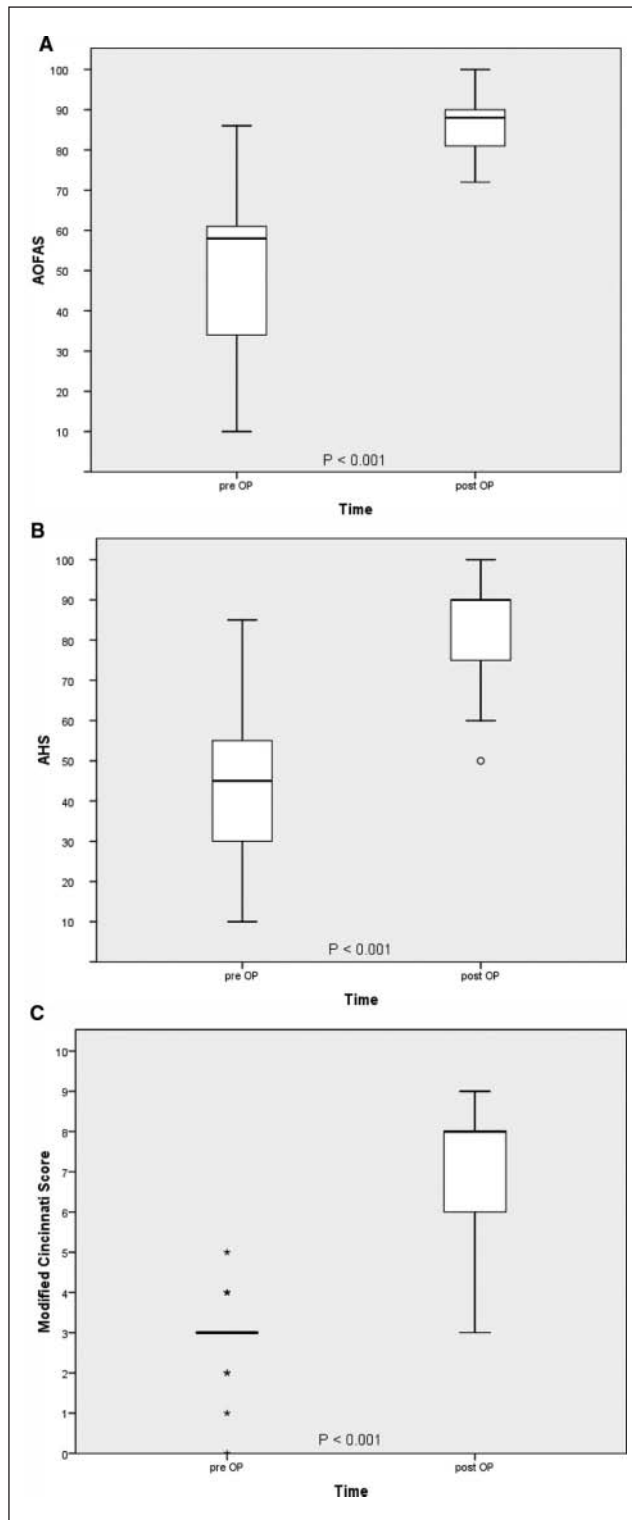
Figure 3. Clinical outcome in various clinical scores (**A-C**). Clinical improvement is highly significant in all score systems. Clinical improvement could be found in all cases.

minor hypertrophy of the graft was observed, and after smoothing the graft, the patient was symptom free. The second patient required removal of a ventral osteophyte of the distal tibia to achieve a greater range of motion postoperatively.

MRI

Morphologic MRI evaluation demonstrated complete defect coverage in all cases (**Table 2**). Defect filling was defined as complete in 3 cases, 4 had moderate hypertrophy, and the remaining 2 cases had near-complete defect filling. All cases had an intact interface of the repair tissue and the adjacent talar cartilage. Fissures occurred in 2 cases; the remaining repair sites had intact surfaces. Interestingly, minor effusion was observed in 5 cases, and 7 cases had signs of bone marrow edema.

The resolution of the T2 maps allowed for ROI analysis with 100 pixels minimum. RT T2 was 30.9 ± 7.9 (22-43) ms, and RC T2 was 37.3 ± 7.5 (27-47) ms. The unpaired double-tailed Student t test demonstrated no significant difference between RT and RC T2 ($P = 0.095$). Relative T2 (rT2) was 0.85 ± 0.21 (0.49-1.26). Please see **Table 2** for details.

Discussion

This study evaluates the mid-term outcome of ACT and MACT using a hyaluronan matrix in the ankle. We are aware of the limited level of evidence associated with a nonrandomized case series study without control and of the limitations of clinical scores as a measurement of surgical treatment; however, there are few data on mid-term results after MACT in the ankle, and we felt that the inclusion of MR analysis yielded valuable information on the composition of the repair tissue.

Both ACT and MACT proved to be safe procedures and provided good to excellent outcomes in the majority of cases. No severe adverse events or graft failures occurred during follow-up.

Significant improvement was found in all clinical scores. The AOFAS predominantly assesses pain, swelling, and symptoms of instability. Both subjective and objective criteria are assessed. The outcome was excellent in 7, good in 7, and fair in 3 cases (82% good and excellent),[46] and all patients reported to be satisfied with the outcome in everyday life activities. The subjective ankle-hindfoot score is similar to the AOFAS but concentrates on subjective criteria; there was a trend toward lower scores, but only 2 cases differed substantially (cases 1 and 6; see **Table 1**). The modified Cincinnati score was used to assess the level of activity; patients 1, 4, and 6 reported moderate limitations

Table 2. Morphologic MRI Evaluation

Case	Age at MRI	Defect Filling (%)	Interface	Surface	Edema	Effusion	AOFAS	RT T2	RCT2	rT2
5	36	100	Complete	Intact	None	No	Good	25	28	0.89
6	35	100	Complete	Intact	Severe	Yes	Fair	37	47	0.78
9	35	75-100	Complete	Intact	Minor	No	Good	29	34	0.88
14	37	75-100	Complete	<50% of RT depth	Moderate	No	Excellent	25	35	0.72
15	36	100	Complete	Intact	Moderate	Yes	Excellent	23	27	0.87
12	27	>100	Complete	Intact	Moderate	No	Good	33	41	0.80
7	21	>100	Complete	<50% of RT depth	None	Yes	Fair	41	44	0.93
4	34	>100	Complete	Intact	Minor	Yes	Good	43	34	1.26
17	24	>100	Complete	Intact	Minor	Yes	Excellent	22	46	0.49
Mean	31.7							30.9	37.3	0.85
Standard deviation	6.0							7.9	7.5	0.21
Min	21							22	27	0.49
Max	37							43	47	1.26

AOFAS = American Orthopaedic Foot and Ankle Score; MRI = magnetic resonance imaging; RC = reference cartilage; RT = repair tissue; rT2 = relative T2.

to daily life and avoided sports (modified Cincinnati score 3 or 4 in 17.6%). Two patients reported limitations to sports (modified Cincinnati score 5 or 6 in 11.7%), and 11 patients reported sport activity on a regular basis with almost no restrictions (modified Cincinnati score 7 or 8 in 64.7%). Case 3 reported regular sports without any restrictions (ACT; more than 8 years post-op).

Clinical results after bone marrow–stimulating techniques in the ankle have high overall success rates. Saxena *et al*.[46] report that in athletes they achieved good to excellent outcomes after microfracture in all cases (AOFAS higher than 80 points; 26 cases, Hepple 1-4 lesions). In 20 cases with Hepple 5 defects treated with autogeneous bone grafts, they report good to excellent outcomes in 90%. The average follow-up period of their series was 32 (24-55) months.

In contrast, Becher *et al*.[47] found good to excellent results in 79% at 5.8 ± 2.0 years in a series of 45 cases with heterogeneous age and body mass index (BMI); they report that BMI correlated with clinical outcome, whereas age did not. In the treatment of OCD, excision curettage and bone marrow stimulation are reported to yield an overall success rate of 85%.[6]

Studies on the clinical efficacy of ACT or Hyalograft mostly concern short- to mid-term outcome or technical aspects. Giannini *et al*.[15] reported on 8 patients with good clinical results at 2 years, Whittaker *et al*.,[16] found good results in 10 cases at 3 years, and Peterson *et al*.[18] found good and excellent results in 75%. A prospective series of 46 cases treated with Hyalograft C reports good and excellent outcomes in more than 80% at 36 months,[48] but long-term outcome has scarcely been reported on. In the current series, the follow-up period was 6 to 11 years in ACT and 2 to 6 years in MACT. The overall outcomes were comparable to the results reported by other investigators, suggesting stable clinical outcome. In light of the results after bone marrow–stimulating surgery in the ankle, it remains to be determined if ACT techniques will actually yield better results in the ankle in the long term.

It may be of interest to note that in contrast to ACT, the MACT technique was feasible without osteotomy. Biopsy from the same joint was successfully used for the isolation of the chondrocytes. In concordance with the findings of Giannini *et al*.,[49] we did not observe any disadvantage or harvest site morbidity related to the biopsy.

The mini-arthrotomy was performed medial or lateral according to the defect location and allowed for good access to the defect. In cases where the defect extended to the dorsal aspect of the talus, we used a scope to facilitate exact debridement. The matrix was fitted by templating of the defect. The implantation of the soft matrix was then carried out easily; in the cases with osteochondral defects (maximum depth 5 mm), multiple layers were used to ensure complete defect filling.

The long-term outcome of cartilage repair in the knee has been found to depend on the composition of the repair tissue; high proteoglycan content is generally assumed to provide more stable tissue and thus provide better outcome in the long term.[34,35,50-53] At this time, histological biopsy evaluation of Hyalograft RT in the ankle is very limited. Only 3 cases after Hyalograft C have been reported in the ankle; hyaline-like RT was reported in all cases, and the International Cartilage Repair Society repair categories were normal, nearly normal, and nearly normal.[48]

A T2 mapping protocol at 3T that allows for high resolutions, allowing for a separate assessment of the talar and tibial cartilage layers, has been reported recently.[54,55] Briefly, T2 relaxation of cartilage is dominated by the dipolar interaction of water molecules[56] and is therefore influenced both by the free water content of the tissue and by collagen anisotropy.[57,58] Evaluation with polarized light microscopy has demonstrated a strong agreement of T2 variation across the cartilage layers and the zonal organization of the cartilage matrix and of cartilage repair tissue.[58,59] T2 is very sensitive, however, and unspecific due to the numerous factors contributing to transverse relaxation in cartilage[60]; relative T2 directly compares the repair tissue to the adjacent native cartilage and has been introduced in the literature to compare repair tissue composition among different cases.[44,45]

In a case series of 12 patients after MACT in the ankle with a mean age of 32.8 ± 8.5 years and post-op follow-up interval of 19.8 ± 12.6 (6-54) months, the T2 values of the talar control cartilage and repair sites were 47.6 ± 9.3 ms and 50.1 ± 8.0 ms, respectively.[54] Interestingly, lower values were found in the current series (**Table 2**). Still, rT2 values indicate that the repair tissue water and collagen are close to adjacent cartilage in most of the cases except for case 17; an rT2 of 0.49 indicates fibrous repair tissue.[39]

Regarding morphologic MRI outcome, defect filling, graft interface, and repair tissue surface can be considered excellent. Mild effusion was found in 5 cases. It is surprising that subchondral edema was found frequently. Minor and moderate edema (below 2 cm in diameter) apparently did not influence the clinical outcome (good or excellent outcomes in the AOFAS); in contrast, patient 6 (severe edema, fair outcome) reported avoiding sports and stress on the ankle. The current sample size is too small to permit a statistical evaluation of a possible relationship between bone marrow edema and clinical outcome. Corresponding MRI analyses after MACT in the knee demonstrate that unfavorable clinical results are indeed associated with the edema.[5]

In summary, ACT and MACT have the potential to provide excellent outcome at mid-term. Good to excellent outcome was found in 82% in this series. Matrix-assisted implantation allows for a less invasive procedure and can

provide good defect filling as well as repair tissue with a water and collagen content similar to the adjacent cartilage. Further studies in higher numbers, however, will be required to further substantiate these results.

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Declaration of Conflicting Interests

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