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Matrix-associated stem cell transplantation (MAST) in chondral defects of the ankle is safe and effective – 2-year-followup in 130 patients

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ABSTRACT

Background: The aim of the study was to assess the 2-year-follow-up of matrix-associated stem cell transplantation (MAST) in chondral defects of the ankle.
Methods: In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral defect that were treated with MAST from October 1, 2011 to July 31, 2013 were analyzed. Size and location of the chondral defects, method-associated problems and the Visual Analogue Scale Foot and Ankle (VAS FA) before treatment and at follow-up were analyzed. Stem cell-rich blood was harvested from the ipsilateral pelvic bone marrow and centrifuged (10 min, 1500 rpm). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide). The matrix was fixed into the chondral defect with fibrin glue.
Results: One hundred and forty-four patients with 150 chondral defects were included in the study. The age of the patients was 35 years on average (range, 12–68 years), 85 (59%) were male. The VAS FA before surgery was 48.5 on average (range, 16.5–78.8). The defects were located as follows, medial talar shoulder, $n = 62$; lateral talar shoulder, $n = 66$ (medial and lateral talar shoulder, $n = 6$), tibia, $n = 22$. The defect size was 1.6 cm^2 on average (range, .6–6 cm^2). 130 patients (90%) completed 2-year-follow-up. The VAS FA improved to an average of 87.5 (range, 62.1–100; *t*-test (comparison with preoperative scores), $p = .01$).
Conclusions: MAST led to improved and high validated outcome scores. No method related complications were registered. Even though a control group is missing, we conclude that MAST is a safe and effective method for the treatment of chondral defects of the ankle.

1. Introduction

The optimal treatment for chondral defects at foot and ankle is still debatable. The current options are distraction, debridement, abrasion, microfracture, antegrade or retrograde drilling, mosaicplasty or osteochondral autograft transfer system (OATS), autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC), allologous stem cell transplantation, allograft bone/cartilage transplantation, or matrix-associated stem cell transplantation (MAST) [1–48]. MAST is a modification of AMIC with a potentially higher concentration of stem cells in the implanted matrix [1]. In the earlier study, 25 patients were included of which 22 had chondral defects at the ankle [1]. We felt that a cohort of 22 patients is not sufficient to prove effectiveness of a new method and therefore enrolled the current study with much higher case number. Then, not only chondral defect at the ankle were included in the earlier study but also at the subtalar and 1st metatarsophalangeal joints which made it difficult to analyze the results of the ankle joint alone. Therefore, the current study was limited to chondral defects at the ankle. Since the ankle is the joint with most chondral defects in the foot and ankle region, the results of that joint are upfront [1]. The aim of this study was to assess the 2-year-follow-up of MAST in chondral defects of the ankle only and with a higher and more sufficient case number than in this previous study [1].

2. Methods

2.1. Technique

MAST was performed as one-stage open procedure associated with other procedures. The indication for surgery was based on

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clinical symptoms as for example pain or instability. The indication for MAST was subjectively made by the surgeon made during initial arthroscopy. MAST was indicated for instable, fragmented or missing cartilage [49]. The other procedures included joint preserving measures such as synovectomy, lateral ligament reconstruction, peroneal tendon debridement/tenolysis, gastrocnemius tendon lengthening and others [1,50–52]. A gastrocnemius tendon lengthening was performed if ankle dorsiflexion was less than 10° with positive Silverskiöld-test [50–52]. A longitudinal medial 3 cm-skin incision was performed above the origin of the gastrocnemius tendon [53]. The fascia was longitudinally incised, and the entire gastrocnemius tendon was cut directly at the origin of the tendon [53]. The lengthened tendon was secured with a single suture in the lengthened position.

The MAST procedure was performed through a medial approach for medial chondral defects and through a lateral approach for lateral defects. When the chondral defect could not be reached without malleolar osteotomies has been done. Medial malleolar osteotomies were performed as single oblique saw cut. Lateral malleolar osteotomies were performed as anterior window cut with the anterior syndesmotic ligament attached to the cut out fragment and the central and posterior syndesmotic ligaments attached to the remaining main fragment. The osteotomized fragments were later fixed with lag screws. The chondral defect was debrided until stable surrounding cartilage was present (Fig. 2a). Subchondral cysts (MRI-stage 5) were cleared out. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone (Fig. 2a), and at the ground of subchondral bone defects. Bone defects of more than 3 mm depth (cysts and others) were filled with autologous cancellous bone harvested from the distal tibia not exceeding the surrounding subchondral bone level. Stem cell-rich blood was harvested during the procedure from the ipsilateral pelvic bone marrow with a Jamshidi needle (10 mm × 3 mm, Cardinal, Dublin, OH, USA) and a special syringe (Arthrex-ACP®, Arthrex, Naples, FL, USA, Fig. 1a) through a stab incision. The syringe was centrifuged (10 min, 1500 rpm). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide®, Geistlich, Baden-Baden, Germany, Fig. 1b and c) that was cut to the size of the cartilage defect roughly before and definitely after (Fig. 1c). The matrix with stem cells was fixed into the chondral defect with fibrin glue (Tissucoll, Deerfield, IL, USA, Fig. 2b). A 10 ch drainage without suction was inserted. Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin). The postoperative treatment included partial weight bearing with 15 kg with orthosis (Vacuped, Oped, Valley, Germany). Motion of the joint with MAST was restricted for two days, and joint motion in the orthosis, i.e. approximately 10° range of motion, was started at day three after surgery. Postoperative consultations were performed at 6 weeks, 3, 12 and 24 months,

2.2. Study design

In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral defect at the ankle that were treated with MAST from October 1, 2011 to July 31, 2013 were analyzed. Patients with bilateral treatment ($n = 25$) or MAST at more than one joint surface, i.e. talus and tibia ($n = 12$) were excluded from the study. No other exclusion criteria were defined. All patients had radiographs (bilateral views (dorsoplantar and lateral) full weight bearing) or PedCAT scan based on the availability of PedCAT after July 2012 [54]. Magnetic resonance imaging (MRI) was obtained before surgery and at follow-up. Before July 2014, "standard" MRI imaging with slice thickness of 3 mm was obtained. From July 2014, MRI with so-called "Cartilage-mapping" with slice thickness of 0.4 mm was obtained. There were no limitations in terms of patient's age and defect size defined. There was no clear and objective definition regarding the combination of defect size, location and age. Visual Analogue Scale Foot and Ankle (VAS FA) was registered [55,56]. The defect size and location was registered. The defects were classified based on MRI [57]. Complications and treatment failure, as for example conversion to ankle joint replacement of arthrodesis were registered. The VAS FA was registered at 2-year-follow-up.

2.3. Statistical analysis

The data was analyzed with SPSS software (IBM SPSS Statistics 23, IBM, Armonk, NY, USA). A unpaired t-test was used for statistical comparison of VAS FA preoperatively and at follow-up. Before using the paired t-test, the data were investigated regarding the distribution and the data were proven to be normally distributed. ANOVA (potential Scheffe Post Hoc test) was used to analyze differences of the follow-up scores for different defect location, size (defect size ≤2 cm or >2 cm) and MRI-stage [57]. The significance level was defined as $p < 0.05$. A power analysis that was carried out before each specific statistical justified sufficient power (>0.8).

3. Results

One hundred and forty-four patients with 150 chondral defects were included in the study. The age at the time of surgery was 35 years on average (range, 12–68 years), 85 (59%) were male. The VAS FA before surgery was 48.5 on average (range, 16.5–78.8). In 70 cases (49%), the right foot was affected. Table 1 shows the suspected cause and suspected mechanism of the chondral defects. Sports-related trauma (42%) was the most common cause, and multiple sprains (61%) the most common suspected mechanism. Fifty-five (37%) had prior surgery including arthroscopic debridement and microfracturing.

The defects were located as follows, medial talar shoulder, $n = 62$; lateral talar shoulder, $n = 66$ (medial and lateral talar shoulder, $n = 6$), tibia, $n = 22$. The defect size was 1.6 cm^2 on average (range, .6–6 cm^2). Seventy-seven (53%) defects were ≤2 cm and 67 (47%) >2 cm. Table 2 shows the MRI-stage of the defects. Most common stages were 1 (cartilage lesion only) in 45 defects (30) and 2a (subchondral fracture with surrounding bone oedema) in 38 (25). Table 3 shows the additional surgical procedures. Synovectomy was performed in all cases, lateral ligament reconstruction in 90% and gastrocnemius tendon lengthening in 60%.

No complications (neuropraxia, stiffness, wound healing problems, thrombosis, infection) or consecutive surgeries were registered until follow-up, One hundred and thirty (90%) patients completed 2-year-follow-up. VAS FA improved to 87.5 (range, 62.1–100; t-test, $p < .01$). Table 4 shows the mean VAS FA differentiated for different chondral defect specification at time of surgery. Different defect location (medial/lateral talar shoulder, tibia), defect size (≤2 cm or >2 cm) or stage did not lead to different follow-up scores (ANOVA, all $p > .05$, Post Hoc test not applicable). Highest scores were registered in defects located at the tibia, size ≤2 cm, and MRI-stage 2a.

4. Discussion

Our score results are favourable and no adverse effects have been registered.

When comparing length and rate of follow-up, our results have the typical 2-year-follow-up with a 90% follow-up rate. Comparison with other studies with the same method is not possible based on the lack of other publications which is typical for new methods.

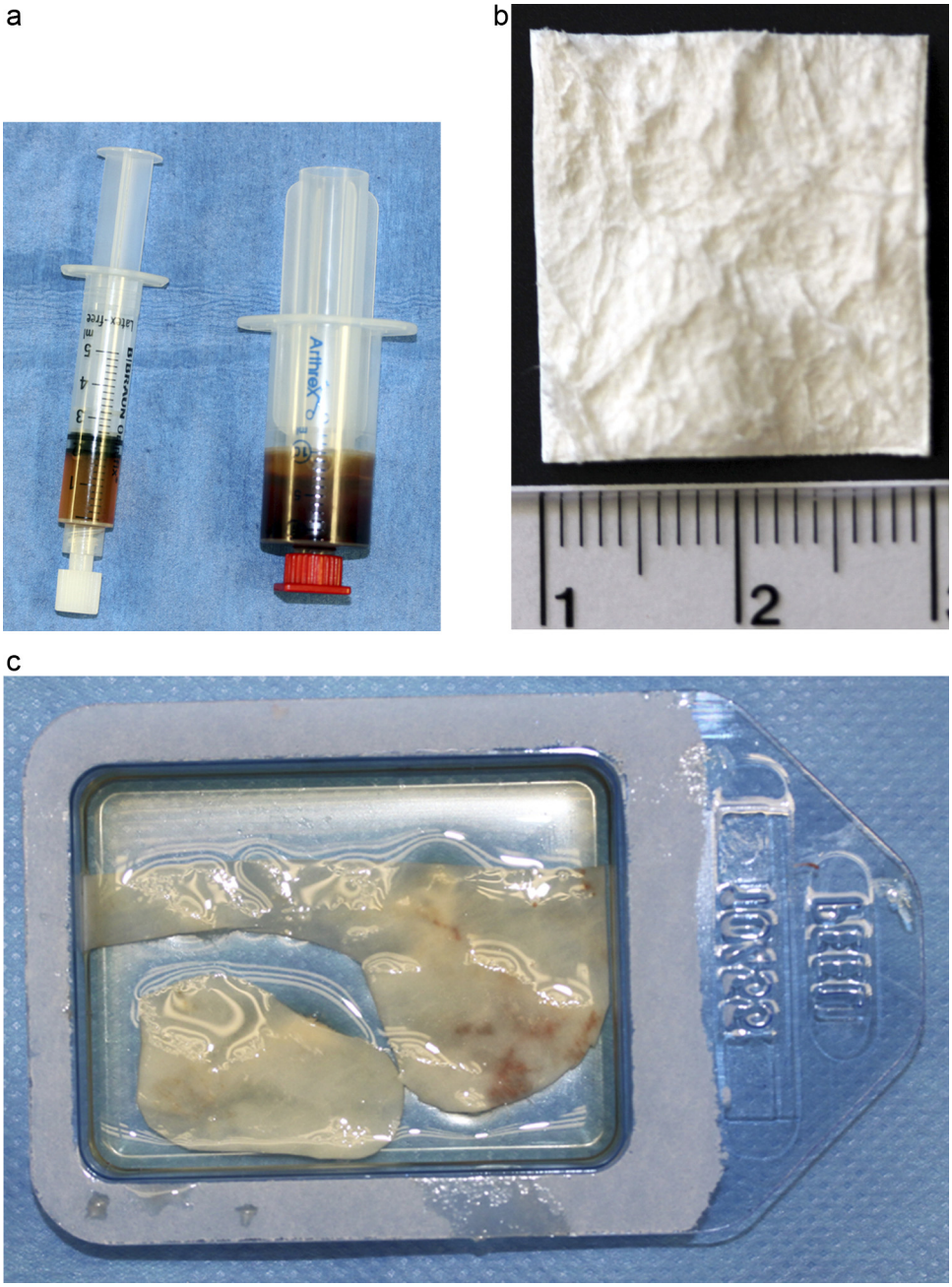

Fig. 1. (a) The syringe system (Arthrex-ACP, Arthrex, Naples, FL, USA). The small syringe (left) is during harvesting and centrifugation in the larger syringe (right). After centrifugation, the supernatant is evacuated with the smaller syringe which is then removed from the larger syringe. (b) Underside of the Chondro-Gide matrix (Geistlich, Baden-Baden, Germany). This matrix contains collagen I and III. The matrix has two layers (bilayer). The superficial layer is waterproof. Different sizes are available. (c) Chondro-Gide matrix after impregnation with the stem-cell rich fluid from the smaller syringe (a – left). The matrix is roughly cut to size before impregnation, and is definitely cut to the correct size after impregnation because the matrix enlarges during impregnation.

Comparison with other studies with different methods is difficultor also not possible, because we are not aware of a single study using a validated outcome score as performed in our study [55,56]. When ignoring the lack of validated outcome score, the comparison with other studies show similar or better results in our study [1–48]. We would still be extremely interested in histological specimens of the transplants [1]. However, no patient was undertaken surgery again until follow-up in which histological specimens could have been harvested. Earlier histological assessment from specimens from the talus gave anecdotal but clear evidence that the transplanted cells could develop or better determine into chondrocytes, and that the implanted collagen matrix stayed in place and acts as a scaffold for the chondrocytes as in "real" cartilage [1]. The same was observed in all specimens that were taken during surgeries in any patient after follow-up ($n = 8$, Fig. 4). We would like to point out that all surgeries were performed after repeated trauma after follow-up. We could not detect outcome score differences between different location, size or MRI-stage of the chondral defects. There was only a slight trend towards smaller defects, located at tibia and lower MRI-stages (1, 2a). However, scores after MRI-stage V (subchondral) cyst were not at all lowest as proposed by other authors [5,30,57]. Consequently, MAST works also for larger defects and "higher" MRI-stages up to lesions with subchondral cyst when the cysts were filled with autologous cancellous bone as in our cohort. Furthermore, it

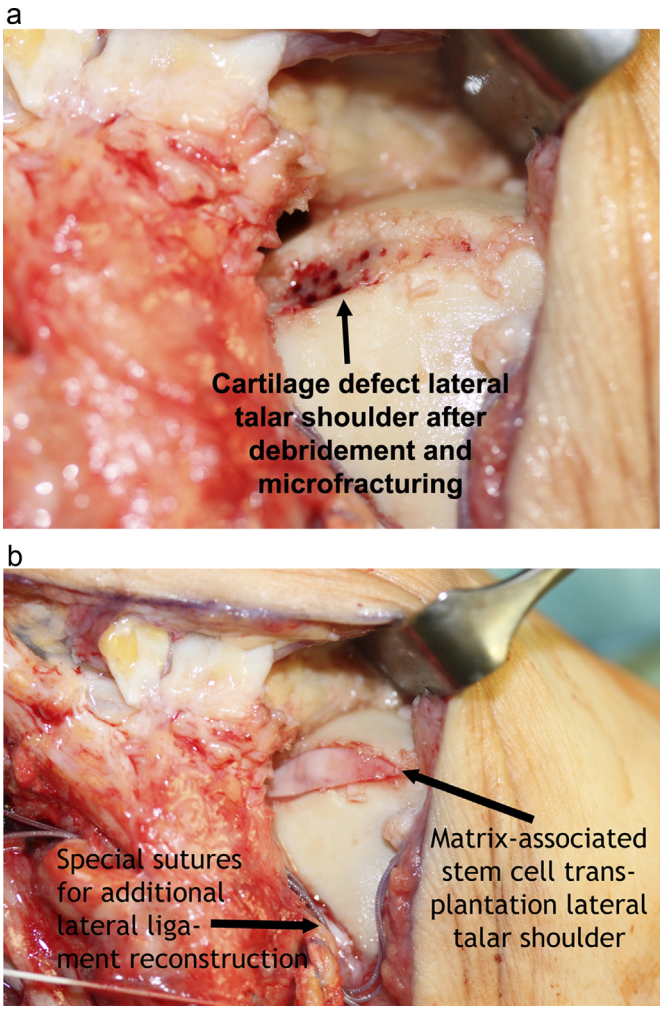

Fig. 2. MAST at lateral talar shoulder. (a) The cartilage defect after debridement and microfracturing and (b) after MAST and lateral ligament reconstruction.

Table 1
Cause and suspected mechanism of chondral lesion.

	n (%)
Cause	
Vehicular accident	12 (8)
Sports-related trauma	60 (42)
Non vehicular/sports-related trauma	50 (35)
Deformity without trauma	6 (4)
Hindfoot/ankle varus	5 (3)
Hindfoot/ankle varus	1 (1)
Other	4 (3)
Unknown	12 (8)
Mechanism	
Fracture	22 (15)
Single sprain	12 (8)
Multiple sprains	88 (61)
Other	2 (1)
Unknown	20 (14)

calls into question if the current MRI based classification looking at the subtalar bone has prognostic value as proposed [57]. We are aware that the reported percentage of gastrocnemius lengthening is high. The indication for gastrocnemius lengthening is not clearly defined and highly debatable. We see more advantages than disadvantages, or higher positive benefit than risk, and this is the main reason for indication.

Table 2
MRI based classification of chondral defects.

Stage	Stage description	*n* (%)
1	Cartilage lesion only	45 (30)
2a	Subchondral fracture with surrounding bone oedema	38 (25)
2b	Subchondral fracture with no surrounding bone oedema	13 (9)
3	Detached but undisplaced fragment	15 (10)
4	Displaced fragment	12 (8)
5	Subchondral cyst	27 (18)

Table 3
Additional procedures performed during surgery in 144 cases.

Procedure	*n* (%)
Arthroscopy	144 (100)
Synovectomy	144 (100)
Debridement/tenolysis peroneal tendons	130 (90)
Lateral ligament reconstruction/augmentation	130 (90)
Gastrocnemius tendon lengthening	86 (60)
Medial malleolus osteotomy	13 (9)
Lateral malleolus osteotomy	2 (1)
Autologous cancellous bone transplantation (under MAST)	19 (13)
Correction of malalignment	6 (4)
Correction above ankle	2 (1)
Correction below ankle	4 (3)

Table 4
VAS FA at 2-year follow-up for different chondral defect specifications at time of surgery.

	n (%)	VAS FA (mean)	ANOVA, *p*
Location			
Medial talar shoulder	52 (49)	89.1	
Lateral talar shoulder	55 (42)	88.4	
Medial *plus* lateral talar shoulder	4 (3)	82.9	
Tibia	19 (15)	89.8	0.15
Size			
≤2 cm	69 (53)	89.2	
>2 cm	61 (47)	85.5	0.23
MRI-stage			
1	39 (30)	88.4	
2a	33 (25)	89.7	
2b	11 (8)	85.4	
3	13 (10)	84.5	
4	11 (8)	83.1	
5	23 (18)	87.0	0.11

4.1. Technical issues

MAST is a combination of stem cell transplantation and AMIC [1]. The advantage in comparison with AMIC which uses peripheral blood is the higher concentration of pluripotent cells or stem cells. No one knows the exact concentration of stem cells which varies for different age and location [1,58]. Rough estimations name 0.1% stem cells as concentration in the peripheral blood and 3% in the pelvic bone marrow in young adults [1,58,59]. This deduces that the cells should be harvested from the pelvic bone marrow which is part of MAST [1]. Centrifugation is a useful method to double the concentration of the cells, and the MAST includes a typical centrifugation (1500 rpm for 10 min) that potentially doubles the concentration of stem cells in the supernatant to 6% [1]. As in MACI, MAST uses a carrier or scaffold for the cells [1]. Different scaffold are available, some with hyaluronic acid, and others with collagen [1]. The introduced method includes a collagen matrix (Chondro-Gide®, Geistlich, Baden-Baden, Germany, Fig. 1b and c) [1]. This scaffold is manufactured out of denaturated collagen from the pig, and contains collagen I and III. The matrix has two layers (bilayer).

The superficial layer is waterproof, and the deep layer is porous [1]. The superficial, waterproof layer should maintain the cell fluid in the defect, and the deep, porous layer should contain and maintain the cells, and should integrate in part with the underlying subchondral bone [1]. The microfracturing is added to add cells and to allow for perfusion from the underlying bone (marrow) [1]. The fibrin glue is added to give sufficient initial stability for early functional after treatment [1]. Our strategy is to fit the matrix as exact and as stable as possible [1]. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology and lower cost [1]. The advantage in comparison with AMIC is the potential higher concentration of stem cells [1]. The advantage of the Chondro-Gide in comparison with other scaffolds/matrices used (hyaluronic acid) is the more physiological content and structure [1]. This matrix gives the initial stability to allow the early stimulation of the transplanted cells by cyclic motion and loading which induces the determination of the transplanted stem cells into chondrocytes [1]. Furthermore, it gives the collagen scaffold which seems to be extremely difficult to determine from stem cells by an in vivo stimulation [1]. The necessity of vivo stimulation and determination calls the adequate after treatment into question. It is unknown how much loading and motion is needed. Based on generally questionable compliance, we protect the operated foot and ankle with an orthosis. In cases without ligament reconstruction (14 of 144) an orthosis would not have been necessary to protect the reconstructed ligaments. Our hypothesis was that the possible motion *in* the orthosis is adequate. The score results and anecdotal histological assessment imply supports this hypothesis [1].

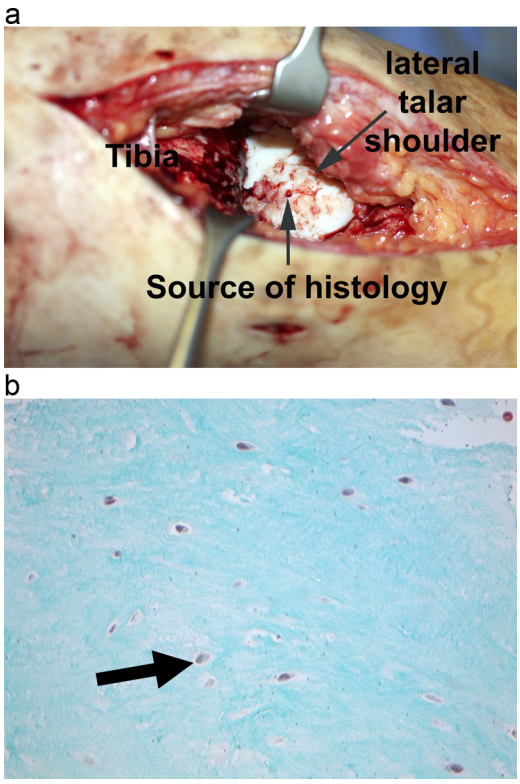

Fig. 4. Histological specimen after MAST at the medial talar shoulder. Same patient as Fig. 2a and 2b. The patient was inconspicuous at 2-year-follow up. Due to a supination trauma 3.5 years after surgery, she underwent surgery. During this surgery a histological specimen was taken at the same location where the matrix-associated stem cell transplantation had been performed (a). The specimen shows a Goldner stain with 40-fold magnification, collagen-specific with verification of collagen (green) (a). Cartilage cells are embedded (arrow). (For interpretation of the references to colour in this legend, the reader is referred to the web version of the article.)

4.2. MRI findings

We utilized MRI for diagnostics including classification [57]. Giannini et al. suggested to use special MRI protocols (T2) for the ankle for evaluation of the tissue at follow-up and created a score from that [19]. They suggested that an integration of both T2 mapping and magnetic resonance observation of cartilage repair scoring permitted adequate evaluation of the repair site in the ankle [19]. Based on our extensive experience, we would like to discuss the diagnostic value of MRI for chondral defects even if we did not investigate the imaging as such. In our earlier study, we noticed a high incoherence between MRI findings and intraoperative (arthroscopic) findings when focusing on the cartilage and not on the subchondral bone situation [1]. This was also described earlier and for other joints [9,13,60,61]. So it seems clear that MRI is able to detect subchondral bone abnormalities but it is much less clear why the investigation of the cartilage is not optimal [57,61]. After having changed from "standard" MRI imaging with slice thickness of 3 mm to so-called "Cartilage-mapping" with slice thickness of 0.4 mm, we immediately realized the reason is simply technical. The normal cartilage thickness at the ankle is around 1 mm. Using an investigating method with a larger slice thickness ("standard" MRI with 3 mm slice thickness) is technically not able to correctly picture cartilage. The created pictures show a full image but the displayed structures between the slices are calculated means from the neighbouring slices. This might be sufficient for subchondral bone structure with a diameter of 3 mm or more but not for cartilage with thickness of less than 2 mm. When we obtained "slices" of 0.4 mm after modifying the MRI at our institution, we immediately noticed the difference (Fig. 3a–c). The cartilage was clearly pictured. Furthermore, fluid content

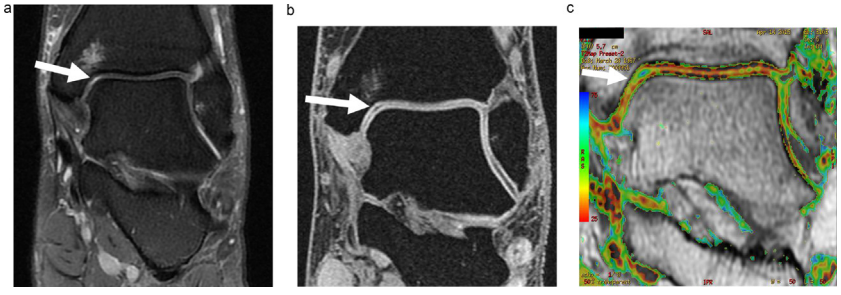

Fig. 3. (a) A coronal MRI reformation of standard T2 specification with 3 mm slice thickness. At the medial tibial plafond (arrow), the cartilage is not clearly visible. (b) A coronal MRI reformation of "Cartilage-mapping" T2 specification with 0.4 mm slice thickness. At the medial tibial plafond (arrow), the cartilage is clearly visible as well as the minimal gap between the tibial and talar cartilage. (c) A colour-coded visualization of the cartilage. At the medial tibial plafond (arrow), the fluid percentage is increased (blue colour). This is a sign of early sign of cartilage damage which often precedes morphological visible damage as in this case (no morphological damage in (b) visible). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

could be measured and displayed (Fig. 3c). Even lacking a scientific investigation, the qualitative interpretation of changed MRI methods with smaller slice thickness implies that the modified technique is much better. We conclude that only MRI with slice thickness of 1 mm or less is able to correctly picture ankle cartilage. Based on our conclusion, we did not include MRI findings in the follow-up analysis because MRI with sufficient technical specifications (thin slice thickness) was not available for the entire follow-up period. Furthermore, the MRI classification is focused on the subchondral bona and not on the cartilage [57].

4.3. Limitations

Limitations of the study are: subjective indication for treatment, unclear influence of associated procedures, no control group, short follow-up, and missing outcome parameter for the created tissue.

The indication for MAST was subjectively made by the surgeon during initial arthroscopy. This is the typical decision-making process also in other studies but does still not follow objective parameters. We believe that "surgical" decision-making is still better than indication based on any kind of imaging based staging with the above described limitations. The indication for MAST was not similar to the indication for surgery as such which was based on clinical symptoms as usual.

The simultaneous additional procedures (Table 3) might also confound the results as in all other studies we are aware of [5,11]. These procedures were considered to be necessary to restore joint function (for example lateral ligament reconstruction in 90% or gastrocnemius tendon lengthening in 60%). Other procedures were performed on a regular basis (for example synovectomy in 100%). It seems unrealistic to diminish the influence of these additional procedures.

A missing control group is always a methodological shortcoming as in many other studies that we cannot invalidate. The follow-up time of 2 years for a modified or new technique seems appropriate. Nevertheless, a longer follow-up would be desirable.

4.4. Future potential [1]

Based our and other results, we do limit the primary surgery to microfracturing and question this treatment as gold-standard. Adding scaffold and more potent "cells" seems to be advantageous without increased risk. Looking in the further future, it seems to be only a question of time until complete cartilage containing chondrocytes and collagen scaffold could be "manufactured" and implanted in the ankle as in other joints [1]. There are promising concepts that could even show good initial clinical results for the ankle joint [1,59,62–64]. It seems clear that only autologous stem cells will be acceptable in the end. Consequently, the stem cell banks need to be established, and each individual might have stem cells in those banks [1]. It is obvious that just injecting non-stimulated stem cells into joints and other structures as actually performed will not allow to create the tissue that should be replaced [1]. In vivo stimulation of the cells is possible as histologically proven [1]. Additionally, the determination of stem cells into cells like chondrocytes is much easier to induce and much faster to complete than to create more complex structures like collagen scaffold [1]. The logical solution of this problem would be to create the entire cartilage in vitro with autologous stem cells [1]. This looks technically demanding but not impossible [64]. The questionable issues are the environment (for example temperature or pH), the stimulation (motion and load), the dose and especially the control of the stem cells [1]. The high potential of the stem cells do also include the risk that undesirable cells and tissues are created, as for example cancer [1]. Facing the fact that all cancer cells have also been stem cells earlier derives this concern [1]. However, if these issues could be resolved not only cartilage but also complete joints could be "manufactured" from autologous stem cells which might then replace the joint replacements techniques that are actually used [1]. The following steps will then be nonsurgical implantations (of "engineered" stem cells) by injection or even medication, and lastly injections or medications that prevent osteoarthritis [1]. For assessment of the cartilage quality, improved MRI techniques with thinner slice thickness and improved analysis of tissue content as for example fluid will allow for better diagnostics and follow-up. Anecdotal convincing histological follow-up might be replaced by that kind of MRI follow-up. This implies also that a new and especially cartilage focused classification needs to be developed for adequate staging based on the thin-slice MRI technology.

In conclusion, MAST for chondral defects at the ankle led to improved and high validated outcome scores. No method related complications were registered. Even though a control group is missing, we conclude that MAST is a safe and effective method for the treatment of chondral defects of the ankle.

Conflict of interest

None of the authors or the authors' institution received funding in relation to this study.

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