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Matrix-associated stem cell transplantation (MAST) in chondral defects of foot and ankle is effective

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ABSTRACT

Background: The aim of the study was to assess the feasibility and clinical results of matrix-associated stem cell transplantation (MAST) and 2-year-follow-up in chondral defects of foot and ankle.
Methods: In a prospective, consecutive, non-controlled clinical follow-up study, all patients with chondral defects, that were treated with MAST from April 1st to November 30th, 2009 were analyzed. The 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 registered and analyzed.
Results: Twenty-six chondral defects in 25 patients were included in the study. The mean age of the patients was 33 years (range, 16–48 years), 18 (72%) were male. The VAS FA before surgery was 49.2 on average (range, 24.3–68.4). The defects were located as follows: medial talar shoulder, $n = 9$; lateral talar shoulder, $n = 13$ (medial and lateral talar shoulder, $n = 1$); distal tibia, $n = 1$; posterior calcaneal facet, $n = 1$; head of 1st metatarsal, $n = 2$. The defect size was 1.1 cm^2 on average (range, .5–6 cm^2). All patients completed 2-year-followup. No complications or consecutive surgeries were registered. The mean VAS FA at follow-up was 94.5 (range, 73.4–100; t-test, $p < .01$).
Conclusions: MAST led to good clinical scores. No 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. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology. The advantage in comparison with AMIC is the potential higher concentration of stem cells.

1. Introduction

The optimal treatment for chondral defects at foot and ankle is 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, or allograft bone/cartilage transplantation [1–47]. Methods like debridement, abrasion, microfracture and retrograde drilling have a limited complexity, expense and morbidity [32,33,42]. However, these methods do not create a normal cartilage but fibrous tissue, or at best fibrous cartilage [32,38,42]. Retrograde drillings might maintain the existing cartilage but cannot create any new cartilage [42]. The effect of distraction on the cartilage remains debatable [44–47]. A positive effect on the cartilage texture could be shown in the animal experiment but not in humans so far [47]. Mosaicplasty or OATS have the advantage of transferring normal cartilage and showed good results [19,21,23,31,34–36]. Considerable disadvantages such as morbidity at the donor site (mostly the knee, up to 30%), mismatch of the cartilage thickness and shape between donor and recipient site, and cumbersome technical issues like often necessary malleolar osteotomies limited the indications and dissemination of these techniques [19,21,31]. Furthermore, OATS did not show better results than microfacture alone which is much easier and quicker to do, and without donor site morbidity [33]. Cartilage cell transplantation techniques (ACI, MACI) utilize autologous cultured chondrocytes that were harvested during an earlier surgical procedure [1,8,11,12,18,20,24,30,38]. The results of these techniques have also been favorable [1,8,11,12,18,20,24,30,38]. However, the disadvantages are enormous. First, an additional surgical procedure for harvesting the cells is needed, and second, the cultivating process is costly and not covered by the health insurances in most countries. ACI, using chondrocytes in fluid form alone, is extremely difficult to perform because the fluid has

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to be fixed within the cartilage defect which is for example done with periosteal flaps that are sutured above and/or below (sandwich technique) the chondrocyte-fluid [24,30]. MACI, using a scaffold matrix, is a useful modification to keep the chondrocytes in the defect and made ACI obsolete in the opinion of most experts [1,11,20]. Still, the most significant disadvantages like two surgical procedures and high cost could not be justified by the results that were clinically not superior to debridement methods [1]. However, the potential of these methods, especially MACI, could be shown in MRI and histological studies in which more physiological cartilage than with debridement or microfracture has been verified [1]. This called into question if "cells" have to be harvested during an earlier surgery. AMIC is using local cells from the underlying bone marrow, cells from the peripherial blood [10,13,22]. The clear advantages in comparison with ACI and MACI are the single surgery and much lower cost [10,13,22]. The latest results of these single stage procedures are comparable to the "real" chondrocyte transplantations, and seem to be more promising overall [10,13,22]. Questionable are the type of cells used, and the techniques for the application and fixation. Some techniques do just inject centrifuged peripheral blood into joints whereas other techniques use centrifuged bone marrow content implanted on hyaluronic acid membranes [10,13,22]. One step further is the use of "real" stem cells (CD 34+) that are currently available as allograft [43]. The use of allograft has several disadvantages such as potential infection and incompatibility (host versus graft and graft versus host). Other unsolved problems are the dosage and control of the stem cell performance or function. Still, the potential of these pluripotent cells (especially when autologous) seems to be the future for cartilage repair (see below). This potential calls especially into question if allologous bone/cartilage transplantation is really an useful option for the further future, or just a temporary trend. The results of these allograft techniques are not convincing but they are mostly used for large cartilage and bone defects that are not comparable with just superficial defects limited to the cartilage [6,9,14,17]. Based on these considerations, comparable techniques with bone plugs or hemiprosthesis seem also to be seminal developments [15].

Matrix-associated stem cell transplantation (MAST) is a modification of AMIC with a potentially higher concentration of stem cells in the implanted matrix. The aim of the study was to assess the feasibility and 2-year-follow-up of MAST in chondral defects of the ankle and additionally in other joints of the foot.

2. Methods

2.1. Technique

MAST was performed as single open procedure associated with other procedures (Table 1). 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) through a stab incision. The syringe was centrifuged (10 min, 1500 rotations per minute (RPM)). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Guide®, Geistlich, Baden-Baden, Germany, Fig. 1a and b) that was cut to the size of the cartilage defect before. The cartilage defect was debrided until stable surrounding cartilage was present (Figs. 2a and 3a). Microfracturing with a 1.6 mm Kirschner wire was performed where the subchondral bone was intact (Figs. 2b and 3b). Autologous cancellous bone transplantation was performed where the subchondral bone was not intact (Fig. 3a and b). The bone graft was harvested through the same approach from the distal tibia (Fig. 3b). The matrix with stem cells was fixed into the chondral defect with fibrin glue (Tissucoll, Deerfield, IL, USA, Figs. 2c, 3c and 4a). If a drainage was used this was without suction. Closure was performed following the local standard. The postoperative treatment included 15 kg partial weight bearing for 6 weeks, normally without orthosis. An orthosis was used only in case of additional ankle ligament reconstruction ($n = 12$). Motion of the joint with MAST was restricted for two days, and physiotherapy with motion of this joint was started at day three after surgery. The patients were instructed to perform motion of the joints with MAST 10 times a day for 10 min. Postoperative consultations were performed at 6 weeks, 3, 12 and 24 months,

Table 1
Additional procedures performed during surgery, grouped to joint addressed with MAST (see Table 3). MTP, metatarsophalangeal joint.

Joint	Procedure	Number
Ankle ($n = 23$)	Arthroscopy	21
	Synovectomy	21
	Debridement/tenolysis peroneal tendons	15
	Lateral ligament reconstruction/augmentation	15
	Autologous cancellous bone transplantation (under MAST)	3
	Medial malleolus osteotomy (defect tibia)	1
Subtalar ($n = 1$)	Removal calcaneus fracture plate	1
	Debridement/tenolysis peroneal tendons	1
	Arthrolysis	1
	Synovectomy	1
	Removal osteophytes	1
MTP 1 ($n = 2$)	Cheilectomy	2
	Bursectomy	2
	Arthrolysis	2
	Synovectomy	2
	Removal osteophytes	2

2.2. Study design

In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral defect that were treated with MAST in foot and ankle from April 1st to November 30th, 2009 were included. Patients with bilateral treatment ($n = 1$) or with MAST at more than one joint surface ($n = 3$) were excluded from the study. No other exclusion criteria were defined. All patients had radiographs (bilateral views in the two standard plains with full weight bearing) and magnetic resonance tomography (MRI) of the region with the involved joints. There were limitations in terms of patient's age and defect size. There was no clear and objective definition regarding the combination of defect size, location and age. The indication was finally made intraoperatively and subjectively by the surgeon. The cause and mechanism of injury was tried to determine. The size and location of the chondral defects, method-associated problems, the rate of sports at least at recreational level was registered, and the Visual Analogue Scale Foot and Ankle (VAS FA) before treatment and at follow-up were registered and analyzed [48,49]. The VAS FA is a validated, foot and ankle specific, questionnaire based, subjective score rating the patients pain, function and other complaints. A paired t-test was used for statistical comparison of VAS FA before surgery 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.

3. Results

Twenty-six chondral defects in 25 patients were included in the study. The age of the patients was 33 years on average (range, 16–48 years), 18 (72%) were male. 18 patients (72%) stated that they performed sports at least at recreational level

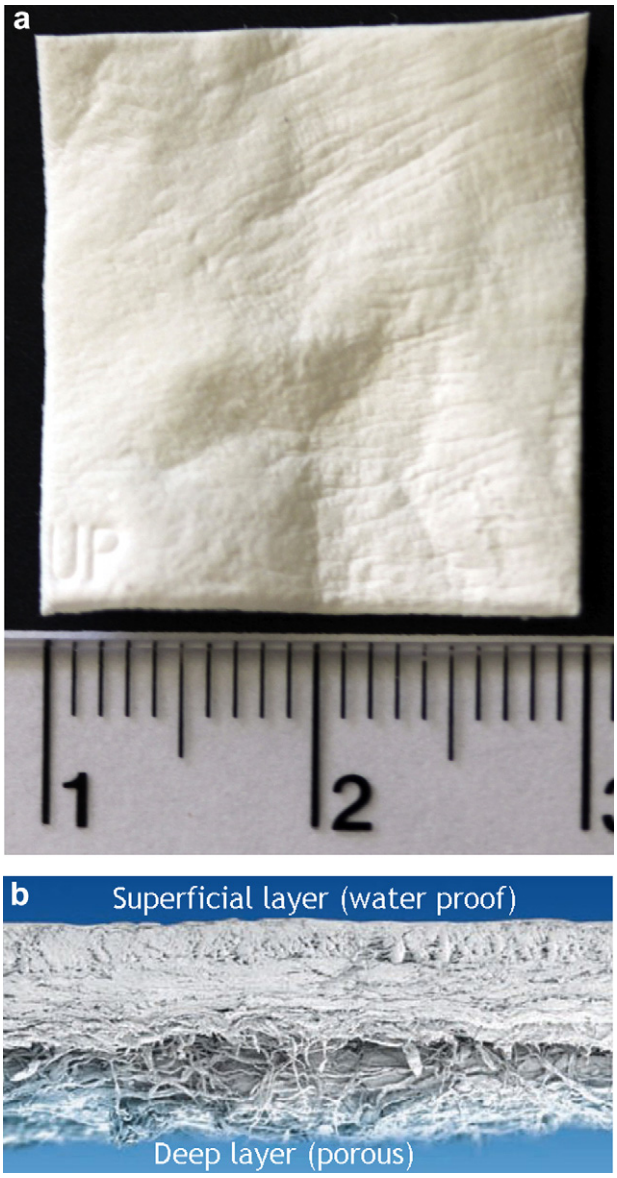

Fig. 1. (a and b) Chondro-Guide® matrix (Geistlich, Baden-Baden, Germany). This matrix contains collagen I and III. The matrix has two layers (bilayer). The superficial layer is water proof (a and b, top). The deep layer is porous (b, bottom). Different sizes are available.

before having symptoms, and 6 (24%) at the time at surgery. Table 2 shows cause and injury mechanism. The most common cause was sports-related trauma ($n = 11$, 42%), and the most common injury mechanism was multiple sprains at the ankle ($n = 10$, 38%). The VAS FA before surgery was 49.2 on average (range, 24.3–68.4) (Table 3). Table 4 shows the location of the defects. The defect size was 1.1 cm^2 on average (range, .6–6 cm^2). Additional autologous bone transplantation under the MAST was performed in 3 cases (medial talar shoulder, $n = 2$ (for example case in Fig. 3a–c; distal tibia, $n = 1$). All patients completed 2-year-follow-up. No complications or consecutive surgeries were registered until follow-up (case shown in Fig. 4 received surgery following repeated injury *after* 2-year-follow-up). The VAS FA improved to an average of 94.5 (range, 73.4–100; *t*-test, $p < .01$) (Table 3). Full weight bearing was achieved in week 7 in all cases. Patients went back to school or work at 4.5 weeks on average (range, 1–12 weeks). 16 patients (64%) stated that they performed sports at least at recreational level at follow-up. This means that 89% (of 18 patients that performed sports before inset of symptoms) returned to sports.

4. Discussion

There are numerous treatment options for cartilage defects of the foot and ankle, of which the majority has been applied of the talus [1–47]. This implies that none of the options described is optimal. Furthermore, the use of these methods in other joints of the foot have not been described so far. This was the reason for us to develop the new method.

4.1. Technical issues

MAST is a modification of AMIC. The advantage in comparison with AMIC which uses local or peripheral blood is the higher concentration of pluripotent cells or stem cells. The exact concentration of stem cells which varies for different age and location is unknown [50]. Rough estimations name 0.1% stem cells as concentration in the peripheral blood and 3% in the pelvic bone marrow in young adults [50,51]. This deduces that the cells should be harvested from the pelvic bone marrow which is part of MAST. 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%. As in MACI, MAST uses a carrier or scaffold for the cells. Different scaffold are available, some with hyaluronic acid, and others with collagen. The introduced method includes a collagen matrix (Chondro-Guide®, Geistlich, Baden-Baden, Germany, Fig. 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 water proof (Fig. 1a and b, top), and the deep layer is porous (Fig. 1b, bottom). The superficial, water proof layer should maintain the cell fluid in the matrix, and the deep, porous layer should contain and maintain the cells, and should integrate in part with the underlying subchondral bone (or bone transplant). The microfracturing is added to add cells and supply from the underlying bone (marrow), as use in microfracture or AMIC alone. The fibrin glue is added to give sufficient initial stability for early functional after treatment. Our strategy is to fit the matrix as exact and as stable as possible. We could not perform this as a complete arthroscopic procedure, and therefore switched to an open procedure with limited approach. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology. The advantage in comparison with AMIC is the potential higher concentration of stem cells. The advantage of the Chondro-Guide® in comparison with other scaffolds/matrices used (hyaluronic acid) is the more physiological content and structure. This matrix gives the initial stability to allow the early stimulation of the transplanted cells by motion and repetitive limited loading which induces the determination of the transplanted stem cells into chondrocytes. Furthermore, it gives the collagen scaffold which seems to be extremely difficult to determine from stem cells by an in vivo stimulation (see below).

4.2. Outcome

Our results are favorable and no adverse effects have been reported so far. None of the above mentioned studies dealing with cartilage restoration used a validated outcome score which makes a comparison with our score results (or clinical outcome) impossible from a scientific point of view [4,28]. When comparing length and rate of follow-up our results have the typical 2-year-follow-up with a 100% follow-up rate which

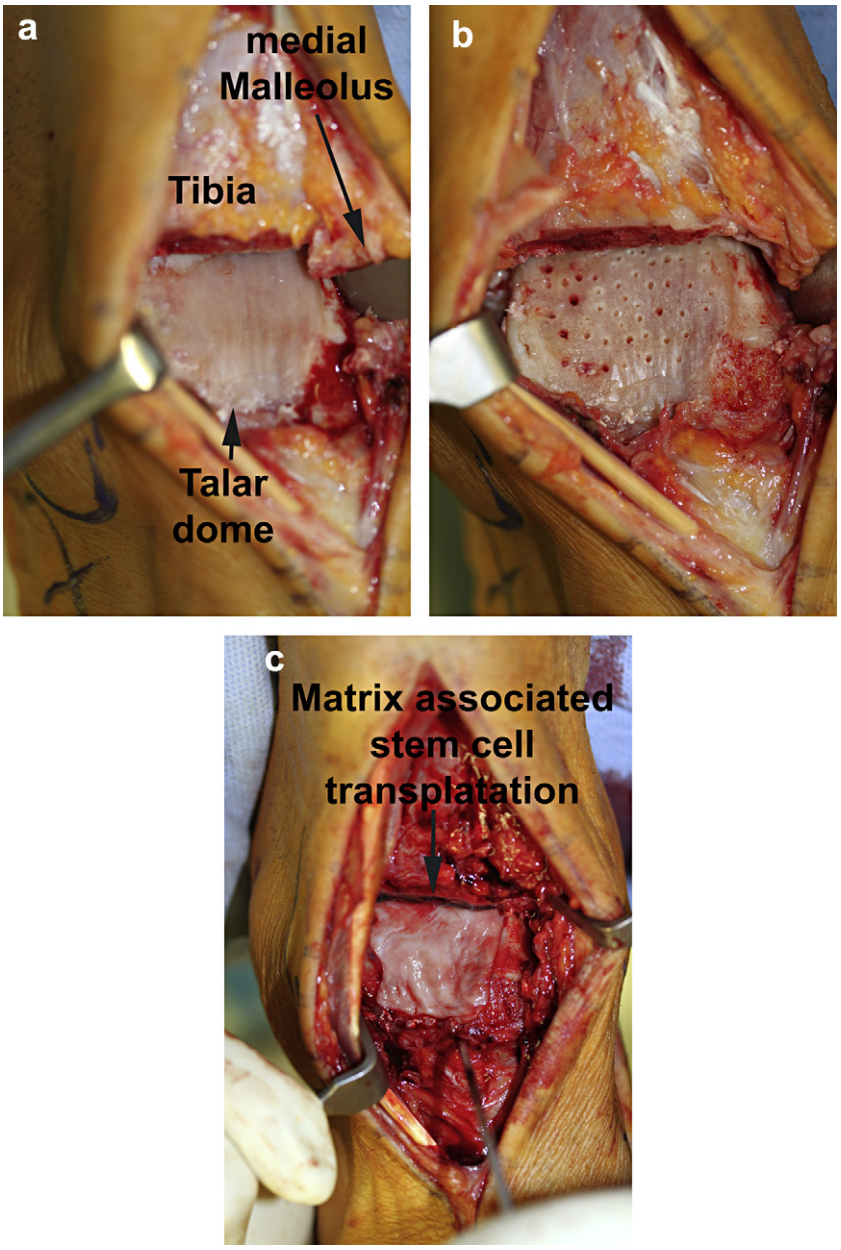

Fig. 2. (a and c) MAST at the talar dome. (a) A large defect (6 cm^2) at the entire talar dome after debridement; (b) the defect after microfracturing; (c) the matrix with cells in vivo.

is not challenged by most other studies [1,4,10,13,28,30]. The rate of return to sport in our study was 89% which is comparable to other studies in which this rate was reported [4,28,30]. We would be extremely interested in histological specimens of all transplants. In view of the lack of clinical symptoms we feel it is very unlikely that further surgery will be necessary in this cohort. As a result histological analysis of the grafts will not probably be possible in the absence of further injury. Exceptional were the two patients that had another injury after the two-year-follow-up (for example Fig. 3). However, these two histological investigations were really exciting because cartilage cells and collagen were found (Fig. 3). This is an anecdotal but clear evidence that the transplanted cells developed or better determined into chondrocytes, and that the implanted collagen matrix stayed in place and acts as a "sceleton" for the chondrocytes as in "real" cartilage. Still, we believe that MAST is just a temporary option on the way to transplanting better cells and scaffold.

4.3. Limitations

Limitations of the study are: small patient number, unclear indication for treatment, multiple surgical sites, multiple associated procedures, no control group, short followup, and missing outcome parameter for the created tissue. We included three different surgical sites (ankle, subtalar, and 1st metatarsophalangeal joints). This mixture might weaken the study from a scientific standpoint. On the other hand, this shows that the introduced technique works well in different joints. To date, we perform at least one third of our MAST procedures in other joints than the ankle and are convinced by the results. The simultaneous procedures (Table 1) might also confound the results as in all other studies we are aware [4]. These procedures are often necessary to restore joint function (for example ligament reconstruction/augmentation in 15 of 21 ankles) and are sometimes performed on a regular basis (for example

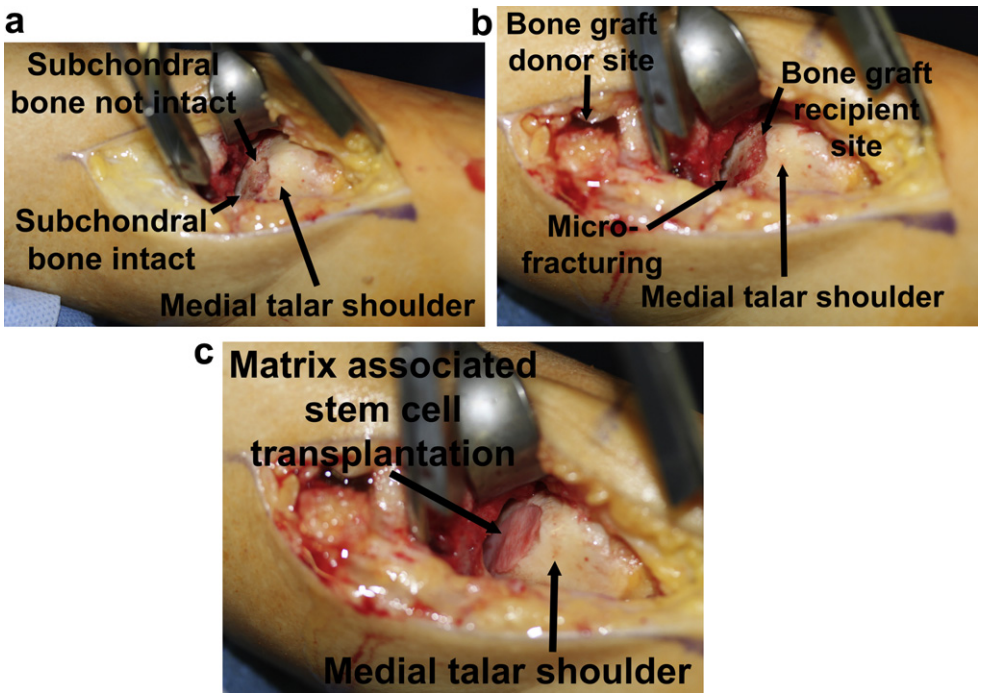

Fig. 3. (a and c) MAST at the medial talar shoulder. (a) A small defect (1.3 cm^3) at the medial talar shoulder after debridement with a defect in the subchondral bone. (b) The defect after microfracturing of the intact subchondral bone and autologous cancellous bone translantation harvested from the distal tibia into the defect of the subchondral bone. (c) The matrix with cells in vivo.

synovectomy in 24 of 24 joints). Consequently, it seem 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 followup time of 2 years for a modified technique seems appropriate and comparable to other studies [1,4,10,13,30]. Nevertheless a longer followup would be desirable. When indicating MAST, we did not follow a clear and objective definition regarding the combination of defect size, location and age. The indication was finally made intraoperatively and subjectiveley by the surgeon. The maximum defect size in our study was 6 cm^2 in the ankle in a young patient (Fig. 2). There are no clear recommendations in the literature regarding defect size and age. Giannini et al. proposed a maximum age of 50 years and a minimum cartilage defect size of 1 cm^2 for their version of AMIC [10,13,22]. However, there is no clear evidence in limiting the indication to a certain defect size or patient age. Regarding assessment of the created tissue, we did not obtain histological specimens (within the study) which would be optimal from a scientific point of view. Giannini et al. suggested to use special MRI protocols (T2) for evaluation of the tissue at follow-up and created a score from that [18]. 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 [18]. We obtained an MRI with T2 mapping in all patients at follow-up but did not find a correlation of the MRI findings and the score (data not shown). Therefore, we used our validated score as principal outcome parameter and not MRI findings [49].

Table 3
Visual Analogue Scale Foot and Ankle (VAS FA) preoperative and at 2-year-followup. MTP, metatarsophalangeal joint; preop, preoperatively.

Joint	VAS FA preop Mean (range)	VAS FA followup Mean (range)	*t*-Test
Ankle ($n=23$)	48.5 (24.3–68.1)	94.8 (73.4–100)	$p<.01$
Subtalar ($n=1$)	52.3 (–)	91.2 (–)	–
MTP 1 ($n=2$)	55.4 (42.3–68.4)	92.7 (88.4–96.9)	$p=0.11$

4.4. Future potential and problems to solve

The logical extension of our and other studies would be prospective randomized controlled studies for comparison of the

Table 2
Cause and mechanism of injury. See Table 4 for exact location of defects. Fracture, undefined mechanism resulting in fracture. MTP, metatarsophalangeal joint. Cause and mechanism of injury are independently listed.

Defect location	Cause	Mechanism
Ankle ($n=23$)	Vehicular accident, $n=4$	Fracture, $n=6$
	Sports-related trauma, $n=11$	Single sprain, $n=2$
	Deformity without trauma, $n=2$	Multiple sprains, $n=10$
	Other, $n=3$	Other, $n=1$
	Unknown, $n=3$	Unknown, $n=4$
Subtalar ($n=1$)	Vehicular accident, $n=1$	Fracture, $n=1$
MTP 1 ($n=2$)	Deformity without trauma, $n=2$	Unknown, $n=2$

Table 4
Location of chondral defects. MTP, metatarsophalangeal joint.

Joint	Bone	Location	Number
Ankle ($n=23$)	Talus	Medial shoulder	7
		Lateral shoulder	12
		Talar dome	1
		Medial and lateral shoulder	1 (2 defects)
	Tibia	Lateral plafond	1
Subtalar ($n=1$)	Calcaneus	Posterior facet	1
MTP 1 ($n=2$)	1st metatarsal	Dorsal 1/2 of head	2
	Total number of defects		26

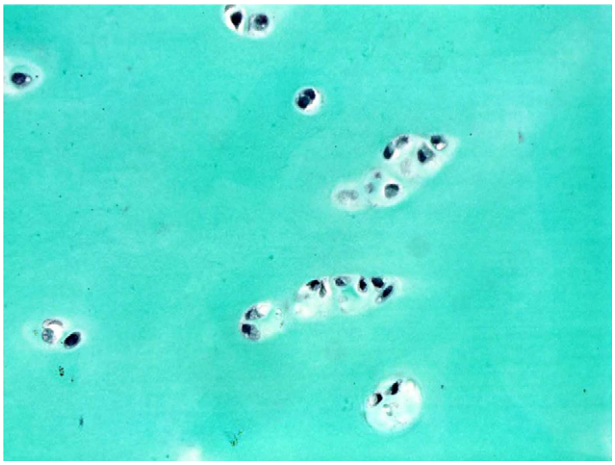

Fig. 4. Histological specimen after MAST at the lateral talar shoulder. The patient was inconspicuous at 2-year-followup. Due to a supination trauma at 2.5 years, he underwent surgery. During this surgery a histological specimen was taken at the same location where the matrix-associated stem cell transplantation had been performed. The specimen shows a Goldner stain 100×, collagen-specific with verification of collagen (here grey, originally green color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

different methods. This is need to clarify if the newer techniques are really better than just debridement of microfracturing, and which is the best treatment option. However, this would be really very difficult to perform because a high number of different study branches (more than ten) are needed: microfracturing only, "scaffold" only, "cells" only, "adjuncts" only (for example fibrin glue), and then different combinations of these as for example microfracturing plus scaffold, microfracturing plus cells, cells plus scaffold and so on. Based on the existing knowledge, it seems to be only a question of time until complete cartilage containing chondrocytes and collagen scaffold could be "manufactured" and implanted. There are promising concepts that could even show good initial clinical results [51–54]. 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. 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. Of course, an in vivo stimulation of the cells is possible as shown by our histology but this takes time. 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. The logical solution of this problem would be to create the entire cartilage in vitro with autologous stem cells. This looks technically demanding but not impossible [54]. 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. The high potential of the stem cells do also include the risk that undesirable cells and tissues are created, as for example cancer. Facing the fact that all cancer cells have also been stem cells earlier derives this concern. 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. 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 at all.

In conclusion, MAST led to good clinical scores. No 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. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology. The advantage in comparison with AMIC is the potential higher concentration of stem cells. It remains unclear if this method is superior to AMIC, and what kind of tissue is created. Prospective randomized controlled studies are needed for comparison of the different methods.

Conflict of interest

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

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