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Autologous matrix-induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects of the first metatarsophalangeal joint

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Abstract

Objective: Chondral restoration in chondral defects of the 1st metatarsophalangeal joint (MTP1) using autologous matrix-induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC).
Indications: Chondral defects MTP1.
Contraindications: Acute infection.
Surgical technique: Thigh tourniquet. Medial approach. Tenolysis of all tendons, arthrolysis, synovectomy. Bursectomy in case of bursitis. Resection osteophytes, optional cheilectomy. Debridement of chondral defects until surrounding cartilage stable. Microfracturing with 1.6 mm K-wire. 15 cc peripheral venous blood harvested with double lumina syringe. Centrifugation (10 min, 1500 RPM). Aspiration of supernatant including the entire fluid layer directly above the erythrocyte layer (peripheral blood concentrate [PBC]). Chondro-Gide matrix was cut to size and impregnated in PBC 3 min (impregnation). Fixation of the matrix into the chondral defect with fibrin glue (AMIC+PBC). Joint motion to ensure stable fixation. Insertion drainage and wound infiltration catheter. Layer wise closure.
Postoperative management: Full weightbearing in a dressing shoe. Joint motion exercise starting at the day of surgery.
Results: The aim of the study was to compare matrix-associated stem cell transplantation (MAST) with AMIC+PBC. Patients who were treated with MAST from October 1, 2011 to July 15, 2016 ($n = 623$) or with AMIC+PBC from July 17, 2016 to March 19, 2018 ($n = 230$) were included. In all, 480 (89%)/176 (89%) patients (MAST/AMIC+PBC) completed 2-year follow-up. The average degree of osteoarthritis was 2.1/2.2. The chondral defect size was 0.9/1.0 cm^2 on average. Visual Analogue Scale Foot and Ankle (VAS FA) and European Foot and Ankle Society score (EFAS score) improved to 72.4/74.1//16.8/17.1 (MAST//AMIC+PBC) at follow-up, respectively. No parameter significantly differed between the MAST and AMIC+PBC cohorts.

Keywords
Chondral defect · Autologous matrix-induced chondrogenesis with peripheral blood concentrate (AMIC+PBC) · Matrix-associated stem cell transplantation (MAST) · First metatarsophalangeal joint

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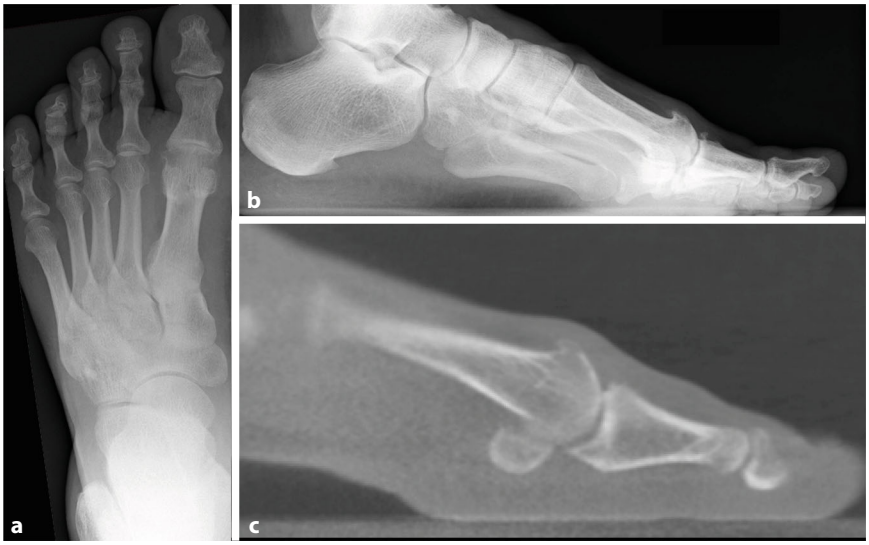

Fig. 1 ▲ Case with hallux rigidus stage 2 [17]. 51-year-old woman; VAS FA 51.1.; EFAS score 12; ROM dorsal extension/plantar flexion 10/0/10°. Preoperative dorsoplantar (**a**) and lateral (**b**) radiographs and 3D-imaging (**c**) with weightbearing showing hallux rigidus stage 2 [17]

Introductory remarks

The optimal treatment for chondral defects of foot and ankle including the first metatarsophalangeal joint (MTP1) is debatable [14, 16]. Principle possible 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, 3, 4, 6–8, 10, 12, 13, 19, 20]. Most of those options have been used first or even exclusively in the ankle [1, 3, 4, 6–8, 10, 12, 13, 16, 19, 20]. MAST was described as a modification of AMIC with a potentially higher concentration of stem cells in the implanted matrix, and also as a completely new method [5, 13]. MAST was also used at MTP1 with encouraging 2-year results and later 4- to 7-year results [11, 14]. However, in 2016, the German government authorities re-categorized MAST, i.e., the included Bone Marrow Aspirate Concentrate (BMAC) for impregnation of the matrix, as stem call manufacturing and heterologous transplantation [13, 15]. Consequently, MAST and all other procedures including BMAC were not "subject to disclosure" as before but "subject to authorization" [15]. Therefore, the authors' institution was not authorized to perform MAST after July 16, 2016, and applied for authorization shortly after [15]. The authorization process is still pending (status March 2020), and no approval for MAST, or any other procedure involving BMAC has been approved in the entire country [15]. Meanwhile, the authors' institution changed the treatment of chondral defects by replacing BMAC as part of MAST to peripheral blood concentrate (PBC) resulting in AMIC+PBC [15]. The effect of replacing MAST (including BMAC) by AMIC+PBC is unclear [15]. Therefore, we conducted a study to compare MAST with AMIC+PBC [15]. As we used MAST before July 16, 2016, and AMIC+PBC after, we could not conduct a prospective controlled study. Consequently, a cohort comparison analysis was performed. This article is focused on the surgical management of AMIC+PBC at MTP1.

Surgical principle and objective

- Restoration of joint function (motion, stability)
- Decrease of symptoms (stiffness, pain)
- Durability

Advantages

- Joint preservation
- Limited surgical morbidity and risk

Disadvantages

- Durability lower than arthrodesis

Indications

- Chondral defects MTP1
- Indication for surgery as such with potential inclusion AMIC+PBC based on clinical symptoms and radiographic findings [16]
- Definite indication for AMIC+PBC procedures during the surgery subjectively made by the surgeon for instable, fragmented or missing cartilage [16]
- No limit regarding chondral defect size

Contraindications

- Acute infection

Patient information

- Standard informed consent
- Use of fibrin glue (blood product)
- Questionable long-term durability
- Membrane dislocation
- Membrane calcification
- Porcine scaffold content
- Additional costs for patients (500 € IGeL [Individuelle Gesundheitsleistungen])

Preoperative work up

- Radiographs with weightbearing dorsoplantar and lateral (◘ **Fig. 1a, b**) or weight-bearing CT (◘ **Fig. 1c**)
- Pedography (◘ **Fig. 2**)

Instruments and materials

- Standard instrument following local standard for forefoot surgery
- Oscillating saw
- 1.6 mm K-wire
- Ronguer
- Sharp spoon
- Double lumina syringe (Arthrex-ACP, Arthrex, Naples, FL, USA)

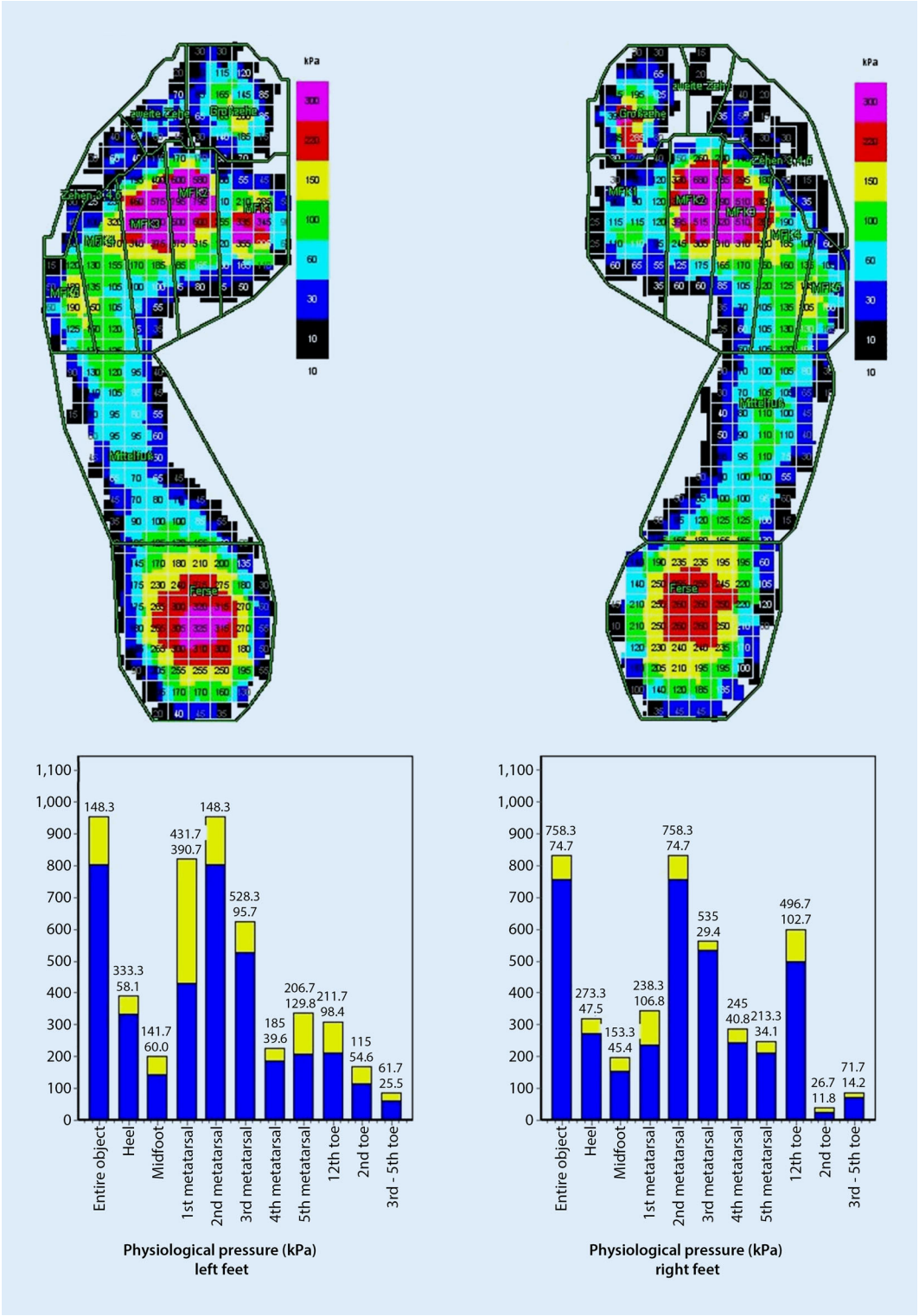

Fig. 2 ◀ Pedographic pattern at 2-year-follow-up (left foot; physiological pressure at the first toe ("12th toe") and first metatarsal head/sesamoids in comparison with normal controls), in comparison with untreated condition (right foot; increased pressure at the first toe ("12th toe") and decreased pressure at the first metatarsal head/sesamoids in comparison with normal controls)

- Collagen matrix (Chondro-Gide, Geistlich, Wollhusen, Switzerland; ◘ **Fig. 3a–c**)
- Fibrin glue (Tissucoll, Deerfield, IL, USA or Tisseel, Baxter, Unterschleissheim, Germany)

Anesthesia and positioning

- General anesthesia favored by author
- Thigh tourniquet
- Elevation of leg (◘ **Fig. 4**)
- Fluoroscope position same side as foot
- Surgeon position opposite side of foot, assistant position same side

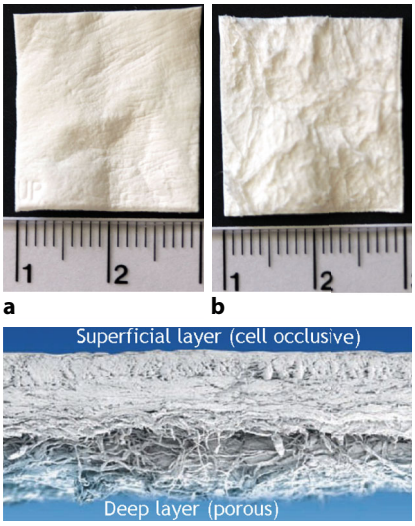

Fig. 3 ▲ Collagen matrix (Chondro-Gide, Geistlich, Wollhusen, Switzerland). This matrix contains collagen I and III. The matrix has two layers (bilayer). The superficial layer is cell occlusive proof (**a**, **c** *top*). The deep layer is porous (**b**, **c** *bottom*). Different sizes are available (scale in cm)

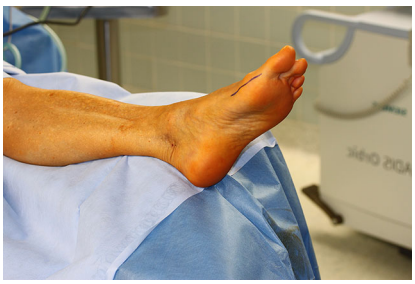

Fig. 4 ▲ Patient positioning. Thigh tourniquet. Elevation of leg. Fluoroscope position same side as foot. Surgeon position opposite side of foot, assistant position same side

Surgical technique

(◘ **Figs. 5**, **6**, **7**, **8**, **9**, **10**)

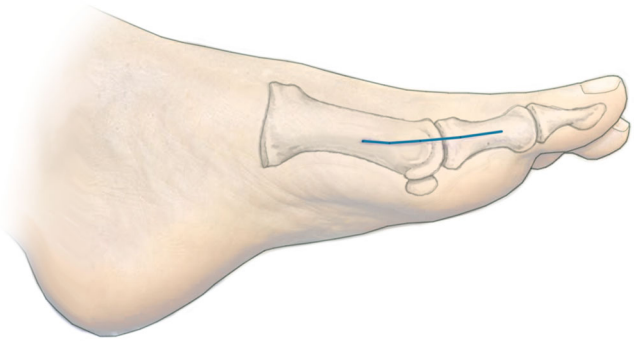

Fig. 5 ◄ Medial approach

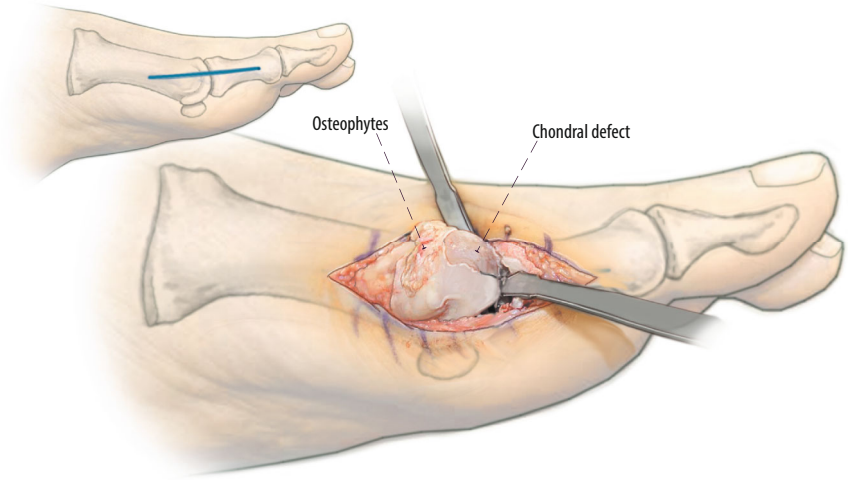

Fig. 6 ▲ Capsulotomy with straight medial cut onto bone. Bursectomy in case of bursitis. Tenolysis of all tendons (*Extensor et Flexor hallucis longus et brevis, Abductor et Adductor hallucis*). Arthrolysis. Synovectomy. Assessment of osteophytes, chondral defect and all four chondral surfaces (metatarsal, phalanx, medial, and lateral sesamoid)

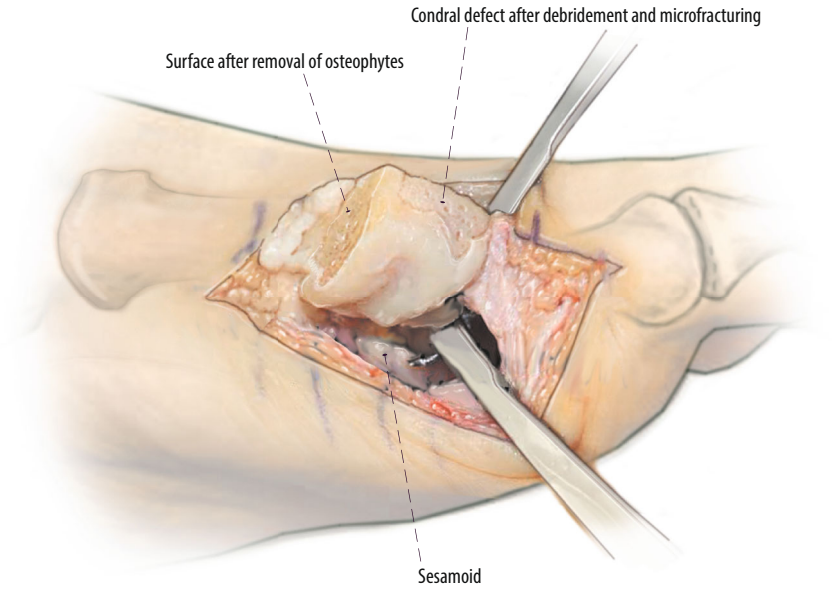

Fig. 7 ▲ Resection osteophytes, optional cheilectomy. Debridement of chondral defect until stable surrounding cartilage is present. Subchondral cysts were cleared out when present [16]. Microfracturing with a 1.6 mm Kirschner wire at intact subchondral bone, and optional at the ground of subchondral bone defects (◘ **Fig. 11b**; depth and distance 3 mm) [16]. Bone defects of more than 3 mm depth (cysts and others) are filled with autologous cancellous bone harvested locally from the resected bone (◘ **Fig. 11c**). Preparation of peripheral blood concentrate (PBC): 15 cc peripheral venous blood is harvested with a double lumina syringe (Arthrex-ACP, Arthrex, Naples, FL, USA). Centrifugation of the syringe (10 min, 1500 rotations per minute) [16]. After centrifugation, the supernatant is aspirated including the entire fluid layer directly above the erythrocyte layer. Thus, PBC is a modification of platelet rich plasma (PRP) and autologous conditioned plasma (ACP) [2, 9, 15, 18]. The difference of PBC to PRP is that for PBC no addition of an anticoagulant, such as citrate dextrose A to prevent platelet activation prior to its use as for PRP [2, 15]. The difference of PBC to ACP is that for PBC the aspirated supernatant (after centrifugation) included the entire fluid layer directly above the erythrocyte layer, whereas ACP includes only the clear fluid above [15, 18]

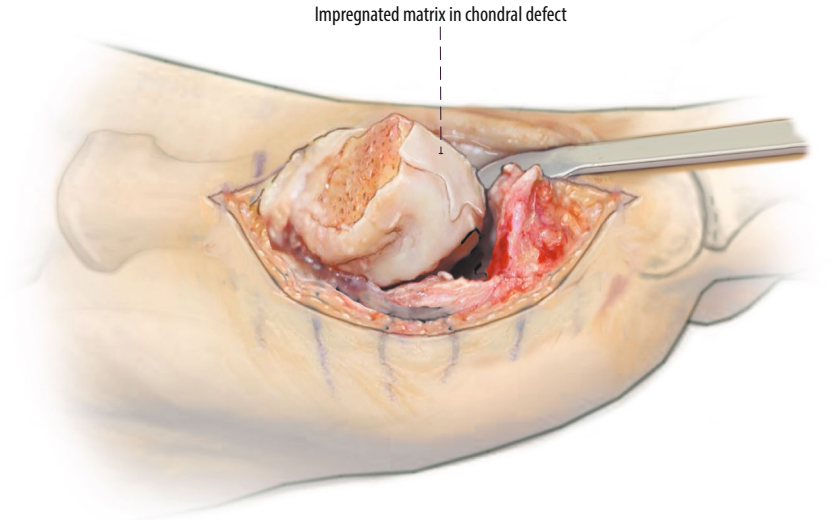

Fig. 8 ▲ Preparation matrix: The supernatant used to impregnate a collagen I/III matrix (Chondro-Gide, Geistlich, Wollhusen, Switzerland) by submerging the matrix completely into the supernatant for 3 min (impregnation) [16]. The matrix is cut to the size of the cartilage defect roughly before and more exact after the impregnation [11, 14]. Fixation of the impregnated matrix with fibrin glue into the chondral defect (AMIC+PBC). When the chondral defect reached the limit of the chondral region, the matrix was placed 3 mm over this limit as shown on the top [16]. In chondral defects comprising the entire chondral surface at the sesamoid, the matrix covered the entire previous chondral surface. Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin)

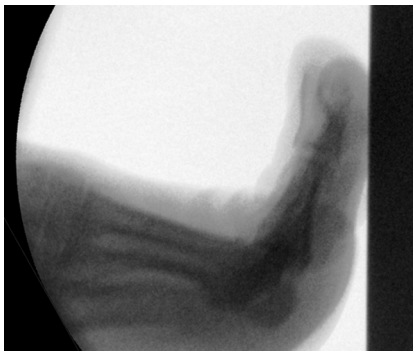

Fig. 9 ▲ Intraoperative fluoroscopy showing 90° dorsal extension at MTP1 (1st metatarsophalangeal joint). The generated image shows the patient the possible dorsal extension. Disadvantages are time spent, cost (draping), and radiation contamination

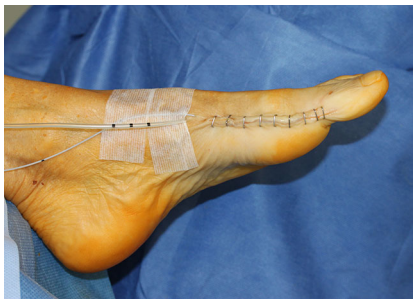

Fig. 10 ▲ Insertion 8 Ch drainage without suction and wound infiltration catheter. Layer wise closure (joint capsule, subcutaneous, skin)

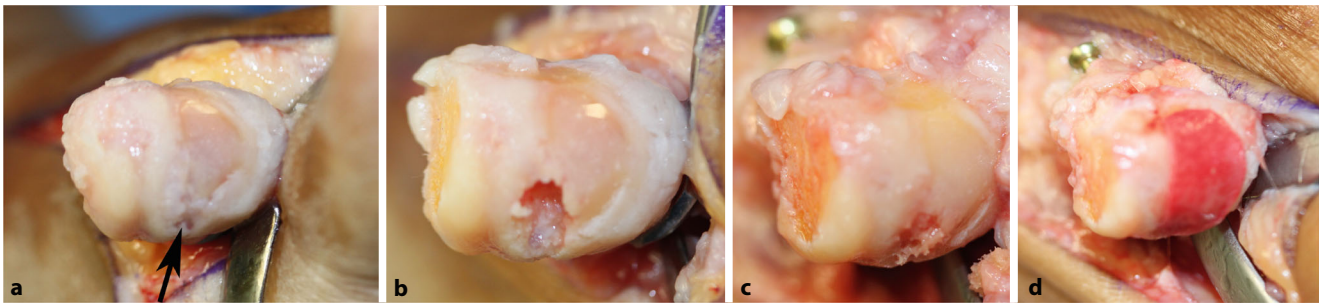

Fig. 11 ▲ Chondral defect at the first metatarsal head in combination with hallux valgus (**a**). The defect was specified as dorsally and plantarly located, size 3.2 cm × 1.1 cm (3.5 cm^2; **a**). A subchondral cyst was detected (*arrow*; **a**). **b** Status after resection of the medial pseudo-exostosis, limited cheilectomy, debridement of the chondral defect and the subchondral cyst. **c** Status after filling of the subchondral cyst with autologous cancellous bone, microfracturing, and distal metatarsal corrective osteotomy. **d** AMIC+PBC in place. (From [16]. Reproduced with permission from © Elsevier. All rights reserved)

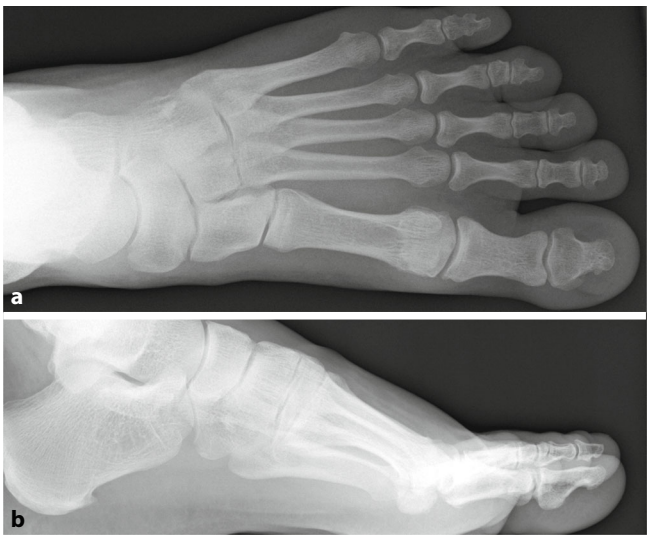

Fig. 12 ◀ Case with preoperative hallux rigidus stage 2 at 2-year follow-up (same case as ◘ **Figs. 1 and 2**). A 56-year-old woman; VAS FA 91.3; EFAS score 21; range-of-motion (ROM) dorsal extension/plantar flexion 110/0/30°. Dorsoplantar (**a**) and lateral (**b**) radiographs with weightbearing at 2-year follow-up showing hallux rigidus stage 0 [17]

Special surgical considerations

(◘ **Fig. 11**)

Postoperative management

- Full weightbearing in dressing shoe when no additional bony correction (dressing shoe [Verbandsschuh], Bort, Weinstadt-Benzach, Germany)
- Full weightbearing in orthotic shoe when additional bony correction (Forefoot Relief Shoe [Vorfußentlastungsschuh mit langer Sohle], Bort, Weinstadt-Benzach, Germany) and splint (Hallufix Hallux Valgus Schiene, Hallufix AG, Grünwald, Germany)
- MTP1 motion active and passive starting at surgical day when no corrective osteotomy. When corrective osteotomy minimal motion under protection of the Hallufix splint.
- Thrombosis prophylaxis with fragmented heparin until full mobilization/weightbearing
- Clinical control at 3 weeks
- Clinical and radiological control at 6 weeks (entire foot dorsoplantar, lateral, and oblique views)
- Yearly clinical and radiological controls (◘ **Fig. 12**)
- Sports such as bicycle ergometer use and athletic training without foot load from day 3, no impact/running sport after skin suture removal; running sports after 6 weeks

Errors, hazards, complications

- Infection: antibiotics, optional (repetitive) debridement
- Stiffness: physiotherapy
- Painful stiffness: revision or conversion to arthrodesis or total joint replacement

Results

The aim of a study was to compare matrix-associated stem cell transplantation (MAST) with autologous matrix-induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects at the first metatarsophalangeal joint (MTP1) [16].

Patients with chondral defect at MTP1 that were treated with MAST from October 1, 2011 to July 15, 2016 ($n = 623$) or with AMIC+PBC from July 17, 2016 to March 19, 2018 ($n = 230$) were included. In all, 1180 (89%)/176 (89%) patients (MAST/AMIC+PBC) completed the 2-year follow-up. Size and location of the chondral defects and the Visual Analogue Scale Foot and Ankle (VAS FA) score and European Foot and Ankle Society score (EFAS score) before treatment and at follow-up were compared (◘ **Table 1**).

In 20%/21% (MAST/AMIC+PBC) of patients no deformities in the forefoot were registered. The average were degree of osteoarthritis was 2.1/2.2 (MAST/AMIC+PBC). The chondral defect size was 0.9/1.0 cm^2 on average (MAST/AMIC+PBC) (◘ **Table 2**). The most common location was metatarsal dorsal (31/33%), and in most patients one defect was registered (71/71%) (MAST/AMIC+PBC; ◘ **Table 2**). Corrective osteotomy of the first metatarsal was performed in 80%/79% (MAST/AMIC+PBC; ◘ **Table 3**). VAS FA/EFAS score were pre-

Table 1 Demographic parameter, preoperative VAS FA and EFAS score, and concomitant forefoot pathology [15]

	MAST	AMIC+PBC	Test, *p*
Age, average (range)	53.6 (8–83)	52.6 (13–78)	t-test, 0.51
Gender, male; *n* (%)	70 (15)	28 (16)	X^2, 0.81
VAS FA, average (range)	48.4 (0–80.4)	46.8 (8.7–79.8)	t-test, 0.18
EFAS score, average (range)[a]	11.6 (2–22)	11.9 (2–22)	t-test, 0.37
Concomitant pathology			
No deformity, *n* (%)	94 (20)	37 (21)	–
HV only, *n* (%)	98 (20)	32 (18)	ANOVA, 0.28
HV plus lesser ray deformity, *n* (%)	288 (60)	107 (61)	–
Degree osteoarthritis, average (range)	2.1 (1–4)	2.2 (1–4)	X^2, 0.43

HV hallux valgus
[a]EFAS score not available for entire MAST cohort

Table 2 Size, location and number (per case) of chondral defects [15]

	MAST	AMIC+PBC	Test, *p*
Size (cm^2), average (range)	0.9 (0.3–6.0)	1.0 (0.2–6.4)	t-test, $p = 0.73$
Location			
Metatatarsal head dorsal, *n* (%)	198 (31)	78 (33)	–
Metatatarsal head plantar, *n* (%)	145 (23)	54 (23)	–
Metatatarsal head dorsal/plantar, *n* (%)	101 (16)	30 (13)	X^2, $p = 0.39$
Medial sesamoid, *n* (%)	146 (23)	56 (24)	–
Lateral sesamoid, *n* (%)	45 (7)	16 (7)	–
Phalanx, *n* (%)	12 (2)	4 (2)	–
Number of defects			
1, *n* (%)	354 (74)	131 (74)	–
2, *n* (%)	93 (19)	31 (18)	–
3, *n* (%)	26 (5)	11 (6)	X^2, $p = 0.73$
4 or more, *n* (%)	7 (1)	3 (2)	–
Total, *n*	647	238	–

Table 3 Additional procedures performed during initial surgery and later revision surgery (cohorts with completed follow-up) [15]

	MAST	AMIC+PBC
Patients in total	*480*	*176*
Additional procedure during initial surgery	*n (%)*	*n (%)*
Synovectomy	480 (100)	176 (100)
Debridement/tenolysis Extensor et flexor hallucis longus et brevis, Abductor/adductor hallucis	480 (100)	176 (100)
Cheilectomy (limited)	480 (100)	176 (100)
Corrective osteotomy 1st metatarsal	386 (80)	139 (79)
Corrective osteotomy 1st phalanx	5 (1)	2 (1)
Arthrodesis 1st tarsometatarsal joint	12 (3)	4 (2)
Corrective osteotomy 2nd–5th metatarsal	288 (60)	107 (61)
Correction arthrodesis PIP 2–3	288 (60)	107 (61)
Autologous cancellous bone transplantation (under MAST)	34 (7)	12 (7)
Revisions		
Joint-preserving surgery	58 (12)	23 (13)
– Including MAST	18 (4)	–
– Including AMIC+PBC	5 (1)	5 (3)
MTP1 fusion	0	0
MTP1 joint replacement	0	0

Case (patient) based analysis. Multiple procedures possible
MTP1 1st tarsophalangeal joint, *PIP* proximal interphalangeal joint

Table 4 Follow-up parameter and values [15]

	MAST	AMIC+PBC	Test, *p*
Overall			
VAS FA, average (range)	72.4 (0–100)	74.1 (19.1–100)	t-test, 0.30
EFAS score, average (range)[a]	16.8 (11–24)	17.1 (11–24)	t-test, 0.51
Degree osteoarthritis, average (range)	0.9 (0–3)	0.8 (0–3)	X^2, 0.48
Without correction			
n	94	36	–
VAS FA, average (range)	83.5 (10.3–100)	81.2 (15.6–100)	t-test, 0.45
EFAS score, average (range)[a]	17.7 (13–24)	18.2 (14–24)	t-test, 0.67
Degree osteoarthritis, average (range)	0.5 (0–3)	0.5 (0–3)	X^2, 0.67
Including Hallux valgus correction			
n	98	35	–
VAS FA, average (range)	67.3 (5.6–100)	68.1 (18.2–100)	t-test, 0.42
EFAS score, average (range)[a]	17.1 (12–24)	17.0 (12–24)	t-test, 0.45
Degree osteoarthritis, average (range)	1.0 (0–3)	0.9 (0–3)	X^2, 0.34
Including Hallux valgus and lesser ray correction			
n	288	105	–
VAS FA, average (range)	64.4 (0–94.5)	63.1 (19.1–92.3)	t-test, 0.25
EFAS score, average (range)[a]	15.9 (11–23)	16.0 (11–24)	t-test, 0.38
Degree osteoarthritis, average (range)	1.1 (0–3)	1.0 (0–3)	X^2, 0.25

[a]EFAS score not available for entire MAST cohort

operatively 11.6/11.9//118.11/116.8 and improved to 72.11/71.1//16.8/17.1 at follow-up (MAST//AMIC+PBC) on average (**Table 4**). No parameter significantly differed between MAST and AMIC+PBC cohorts.

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Declarations

Conflict of interest. M. Richter is consultant of Geistlich.

All relevant ethical guidelines have been respected. Approval from the ethics committee is not available and not necessary. No data were collected for the study results. Only data that had been collected in the context of patient care were evaluated anonymously.

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Zusammenfassung

Autologe Matrixinduzierte Chondrogenese mit peripherem Blutkonzentrat (AMIC+PBC) bei chondralen Defekten am Großzehengrundgelenk

Operationsziel: Wiederherstellung des Knorpels bei Knorpeldefekten im Großzehengrundgelenk (GZG) mittels Autologer Matrixinduzierter Chondrogenese mit peripherem Blutkonzentrat (AMIC+PBC)
Indikationen: Knorpeldefekte im GZG
Kontraindikationen: Akute Infektion
Operationstechnik: Oberschenkelblutleere. Medialer Zugang. Tenolyse aller Sehnen, Arthrolyse, Synovektomie. Bei Bursitis Bursektomie. Osteophyten-Resektion, ggf. Cheilektomie. Debridement des Knorpeldefekts bis stabile „Knorpelschultern" im Randbereich bestehen. Mikrofrakturierung mit 1,6 mm K-Draht. Entnahme 15 ml peripheres Blut mit Doppellumenspritze. Zentrifugation 10 min mit 1500 U/min. Entnahme des Plasmas plus Grenzschicht oberhalb der Erythrozyten (Peripheres Blutkonzentrat [PBC]). Zuschneiden einer Chondro-Gide-Matrix auf Knorpeldefektgröße und Imprägnieren mit PBC für 3 min. Einkleben der imprägnierten Matrix mit Fibrinkleber in den Knorpeldefekt (AMIC+PBC). Gelenkbewegung zur Überprüfung der stabilen Fixierung. Einlage Redon und Wundinfiltrationskatheter. Schichtweiser Verschluss.
Weiterbehandlung: Vollbelastung im Verbandschuh. Bewegungsübungen ab OP-Tag.
Ergebnisse: Das Ziel der Studie war der Vergleich der Matrixassoziierten Stammzelltransplantation (MAST) mit AMIC+PBC. Eingeschlossen wurden Patienten, die 01.10.2011-15.07.2016 mit MAST ($n = 623$) oder 17.07.2016–19.03.2018 mit AMIC+PBC ($n = 230$) behandelt wurden. 480 (89 %)/176 (89 %) Patienten (MAST/AMIC+PBC) wurden nach 2 Jahren nachuntersucht. Das Arthroseausmaß war 2,1/2,2 im Durchschnitt. Die Defektgröße war 0,9/1,0 cm^2 im Durchschnitt. Der Visuelle Analogskala Fuß und Sprunggelenk Score (VAS FA) und der European Foot und Ankle Society Score (EFAS Score) verbesserten sich zum Zeitpunkt der Nachuntersuchung auf jeweils 72,4/74,1//16,8/17,1 (MAST//AMIC+PBC). Parameterunterschiede zwischen den MAST/AMIC+PBC Kohorten bestanden nicht.

Schlüsselwörter
Knorpeldefekt · Autologe Matrixinduzierte Chondrogenese mit peripherem Blutkonzentrat (AMIC+PBC) · Matrixassoziierte Stammzelltransplantation (MAST) · Großzehengrundgelenk