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Autologous Matrix induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC+PBC) in chondral defects of the first metatarsophalangeal joint - 7-year follow-up

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ABSTRACT

Background: The aim of the study was to assess the 7-year-follow-up (7FU) after Autologous Matrix Induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC+PBC) in chondral defects at the first metatarsophalangeal joint (MTP1).

Material and methods: In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral lesion at MTP1 that were treated with AMIC+PBC from April 1, 2009 from July 17, 2016 to May 21, 2017 were included. Size and location of the chondral lesions, the Visual-Analogue-Scale Foot and Ankle (VAS FA) and the European Foot and Ankle Society Score (EFAS Score) before treatment and at 5FU were analysed and compared with previous 2- and 5-year-follow-up (2FU/5FU). Peripheral Blood Concentrate (PBC) was used to impregnate a collagen I/III matrix (Chondro-Gide, Wolhusen, Switzerland) that was fixed into the chondral lesion with fibrin glue.

Results: One hundred and ninety-eight patients with 228 chondral defects were included. In 21 % of patients no deformities in the forefoot were registered. The average degree of osteoarthritis was 2.2. The chondral defect size was 1.0 cm^2 on average. The most common location was metatarsal dorsal (22 %), and in most patients one defect was registered (74 %). Corrective osteotomy of the first metatarsal was performed in 79 %. 176 (89 %)/164 (82 %)/159 (80 %) patients completed 2FU/5FU/7FU VAS FA/EFAS Scores were preoperatively 46.8/11.9 and improved 74.1/17.1//75.0/17.2//72.8/17.5 at 2FU/5FU/7FU on average. No parameter significantly differed between 2FU/5FU/7FU (ANOVA, $p > 0.05$).

Conclusions: In conclusion, AMIC+PBC as treatment for chondral defects at MTP1 as part of joint preserving surgery led to improved and high validated outcome scores at 7FU. The lack of significant differences between 2-year (2FU), 5-year (5FU), and 7-year (7FU) outcomes suggests plateaued benefits.

1. Introduction

The optimal treatment for chondral defects at foot and ankle including the first metatarsophalangeal joint (MTP1) is debatable[1–4]. 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) [3–15]. MAST showed good results up to 7-year follow-up[1,3,4,16]. In 2016, the local government re-categorized MAST, i.e. the included bone marrow aspirate concentrate (BMAC) for impregnation of the matrix, as stem call manufacturing and heterologous transplantation[2,4,7,17]. Consequently, MAST and all other procedures including BMAC were not "subject to disclosure" as before but "subject to authorization"[2,4,17]. Therefore, the authors´ institution was not authorized to perform MAST after July 16, 2016[2,17]. Consequently, the method was changed by replacing BMAC as part of MAST to Peripheral Blood Concentrate (PBC) resulting in AMIC+PBC[2,17]. The effect of replacing MAST (including BMAC) by AMIC+PBC was unclear and a study was conducted to compare MAST with AMIC+PBC[2,17]. AMIC+PBC led to similar improved and high validated outcome scores at 2-year follow-up (2FU) as MAST[2]. No method related complications were registered[2].

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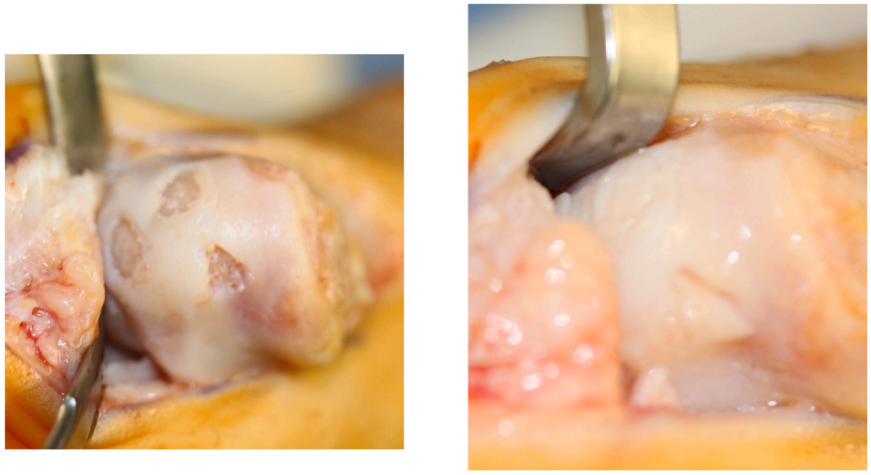

(a) (b)

Fig. 1. a - b[4]. Three chondral defects at the first metatarsal head (Fig. 1a). One defect was specified as dorsally located, size 1.0 cm x 0.7 cm (1.7 cm^2); one as plantarly located, size 0.7 cm x 0.7 cm (0.5 cm^2); one as dorsally and plantarly located, size 0.9 cm x 0.6 cm (0.5 cm^2); (Fig. 1a). Fig. 1b shows the three matrices in place.

Autologous Matrix Induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC+PBC) led to improved and high validated outcome scores at 5-year follow-up[2,4]. Longer follow-up was considered to be important[4]. Therefore, the initial study cohort was followed until 7-year follow-up (7FU). The aim of this study was to assess the 7FU of AMIC+PBC and comparison with earlier 2FU/7FU[2,4].

2. Material and methods

In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral lesion at MTP1 that were treated with AMIC+PBC from April 1, 2009 from July 17, 2016 to May 21, 2017 were included[2].

2.1. Inclusion criteria[2]

The only inclusion criteria were AMIC+PBC at MTP1. 220 patients were eligible for inclusion.

2.2. Exclusion criteria[2]

Exclusion criteria were bilateral treatment (n = 22 patients (14 %)), incomplete 2FU (n = 22 patients (11 %)), revision including arthrodesis/total joint replacement of MTP1 (n = 6/2 patients (2 %/1 %)). Patients with revisions including joint preserving procedures were not excluded. No other exclusion criteria were defined.

2.3. AMIC+PCB indication and techniques[2]

The indication for surgery as such with potential inclusion of AMIC+PBC was based on clinical symptoms and radiographic findings [2]. The definite indication for AMIC+PBC procedures during the surgery was subjectively made by the surgeon for instable, fragmented or missing cartilage[2]. The other procedures included joint preserving measures such as corrective osteotomies, cheilectomy, tendon debridement/tenolysis, and others[2]. The AMIC+PBC procedure was performed through a medial approach (Fig. 1 and 3)[2]. The chondral defect was debrided until stable surrounding cartilage was present. Subchondral cysts were cleared out[1,18]. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone, and at the ground of subchondral bone defects[19]. Bone defects of more than 2 mm depth (cysts and others) were filled with autologous cancellous bone harvested locally from the resected bone. 15cc peripheral venous blood was harvested with the same special syringe (Arthrex-ACP, Arthrex, Naples, FL, USA)[2]. The syringe was centrifuged (10 minutes, 1500 rotations per minute)[2]. After centrifugation, the supernatant was aspirated including the entire fluid layer directly above the erythrocyte layer. PBC is a modification of Platelet Rich Plasma (PRP) and Autologous Conditioned Plasma (ACP)[2,20–22]. 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[2,22]. 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 the only the clear fluid above[2,20]. The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide, Geistlich, Wolhusen, Switzerland) by submerging the matrix completely into the supernatant for 2 minutes (impregnation)[2]. The matrix was cut to the size of the cartilage defect roughly before and more exact after the impregnation[2]. When the chondral defect reached the limit of the chondral region, the matrix was placed 2 mm over this limit[2]. In chondral defects comprising the entire chondral surface at the sesamoid, the matrix covered the entire previous chondral surface[2]. Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin)[2]. The postoperative treatment included full weight bearing with a dressing protection orthosis (Verbandschuh, Bort, Weinstadt-Benzach, Germany) without splint in cases without corrective osteotomy. The dressing protection orthosis was used as long as the foot with dressing did not fit in a standard shoe. Active and passive MTP1 dorsiflexion was started at the day of surgery. In cases with corrective osteotomies, the postoperative treatment included full weight bearing with an orthosis unloading the forefoot (Forefoot Relief Shoe, Bort, Weinstadt-Benzach, Germany) for 6 weeks and splint with hinge (Hallufix Hallux Valgus Schiene, Hallufix AG, Grünwald, Germany) for 2 weeks[2]. Limited active and passive MTP1 dorsiflexion with the splint was started at the day of surgery. Postoperative consultations were performed at 6 weeks, 2, 12 months and then yearly.

2.4. Follow-up[2]

2FU/5FU/7FU was defined as follow-up 22–26/56–64/80–88 months postoperatively.

2.5. Parameter[2]

Before surgery and at follow-up, radiographs (bilateral views (dorsoplantar and lateral) with full weight bearing and/or

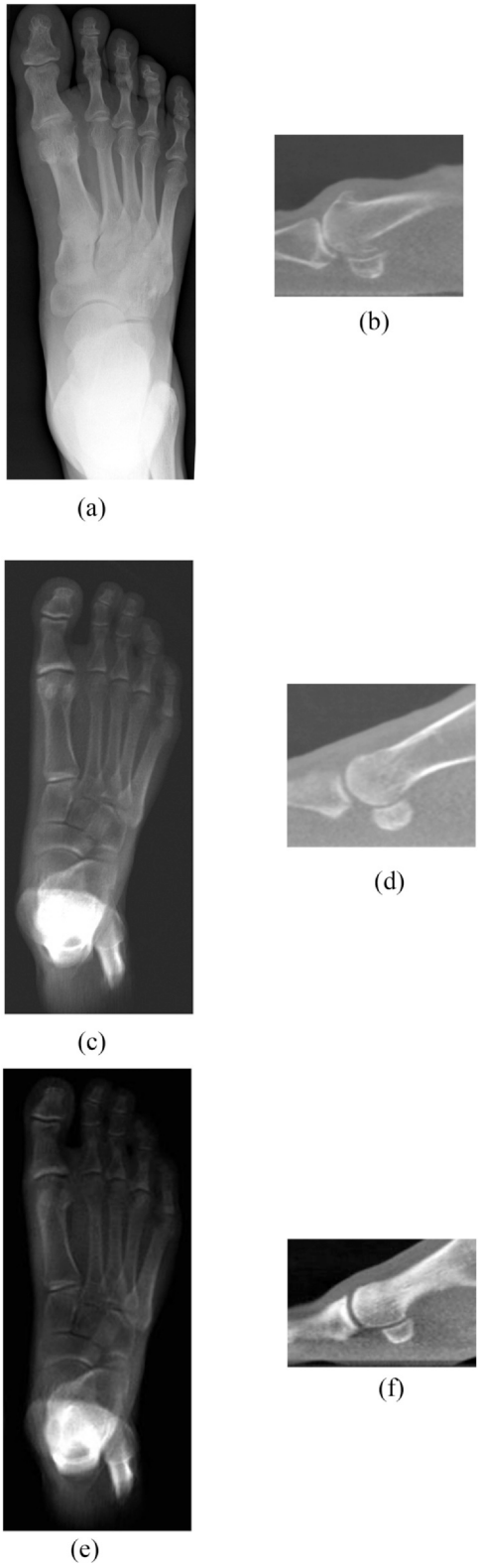

Fig. 2. a - e. Same case a Fig. 1a - b. Preoperative dorsoplantar radiograph with weightbearing (Fig. 2a) and WBCT parasagittal reformation (Fig. 2b) showing osteoarthritis stage 2[4]. Dorsoplantar virtual radiograph with weightbearing reformatted from WBCT (Fig. 2c) and WBCT parasagittal reformation (Fig. 2d) at 5FU and at 7FU (Fig. 2e and f) show osteoarthritis stage 1[4,25].

Weightbearing Computed Tomography (WBCT) scans were obtained (Fig. 2a - f. 3 a and 3 e)[2]. Visual Analogue Scale Foot and Ankle (VAS FA) and European Foot and Ankle Society Score (EFAS Score) were registered[23,24]. The EFAS Score was available at the authors´ institution before official publication because the institution was included in the development and validation of the score[23]. The defect size and location were assessed intraoperatively. The defects were classified as dorsal when located above a virtual horizontal line at 50 % of the metatarsal head height or diameter, plantar when located below that line, or both when crossing the line[18]. The degree of osteoarthritis was classified in four degrees[25]. Complications and treatment failure were registered. The resolution of the MRI available at our institution was 3 mm for the forefoot region. Reflecting the cartilage thickness in the 1st MTP with 1–2 mm, we were not able to assess the cartilage with MRI and did not use it during the treatment and also not for the study.

2.6. Statistical analysis

The data was analysed with SPSS software (IBM SPSS Statistics 25, IBM, Armonk, NY, USA). An unpaired *t*-test was used for statistical comparison of VAS FA and EFAS Score preoperatively and at follow-ups. Before using the paired *t*-test, the data were investigated regarding the distribution and the data were proven to be normally distributed. Oneway ANOVA was used for parameter comparison between 2FU/5FU/7FU. The significance level was defined as $p < 0.05$. For significant differences of the ANOVA test post-hoc Scheffe test was planned. A power analysis that was carried out before each specific statistical justified sufficient power (> 0.8).

3. Results

One hundred and ninety-eight patients with 228 chondral defects were included. The mean age 52.6 years (range, 13–78), 41 % (n = 81) were male. The mean VAS FA 46.8 (range, 8.7–79.8) and the mean EFAS Score 11.9 (range, 2–22). The average degree of osteoarthritis was 2.2. Table 1 shows size, location and number of the chondral defects[2]. The chondral defect size was 1.0 cm^2 on average. The most common location was dorsal metatarsal head (22 %), and in 74 % one defect was registered (Table 1). Corrective osteotomy of the first metatarsal was performed in 79 %. 22 (12 %) patients were revised with joint-preserving surgery including joint debridement and implant removal, and 5 (2 %) including another AMIC+PBC until 2FU. No further revisions were registered after 2FU until 5FU/7FU (Table 2). No AMIC+PBC related adverse effects have been registered.

3.1. Follow-up

176 (89 %)/164 (82 %)/159 (80 %) patients completed 2FU/5FU/7FU. Among the patients that completed 7 FU (n = 159), Hallux rigidus without deformity was registered in n = 33 (21 %), isolated Hallux valgus (HV) in n = 29 (18 %), and HV plus lesser ray deformity in n = 97 (61 %). Table 2 shows the additional surgical procedures[2]. Table 3 shows the follow-up parameter and subgroups without correction and with correction of the 1st ray or the 1st and other rays. The highest scores and lowest degree of osteoarthritis occurred in the groups without correction.

3.2. Comparison 2FU/5FU/7FU

The parameters of 2FU/5FU/7FU did not differ in all above listed parameters (each $p > 0.05$) (Table 3).

4. Discussion

This is the first study analysing 7FU after AMIC+PBC in chondral defects of MTP1. An ongoing prospective data acquisition of all surgically treated patients including yearly follow-up at the authors´ institution is the basis for this ongoing analysis[2,4].

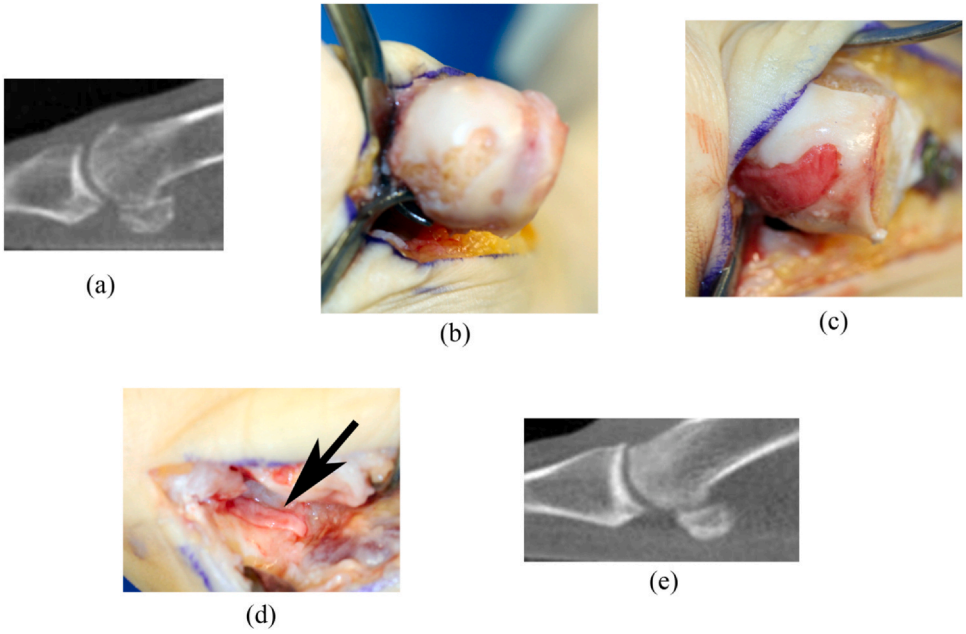

Fig. 3. a - e. Hallux valgus et rigidus stage 2 with joint space collapse between metatarsal head and medial sesamoid in WBCT parasagittal reformation (Fig. 3a)[4,25]. One chondral defect was specified as centrally located at the metatarsal head, size 2.0 cm x 0.7 cm (3.4 cm^2) (Fig. 3b and c) and one as plantarly located at the medial sesamoid, size 1.0 cm x 0.4 cm (0.4 cm^2) (d). The defects were debrided and microfractured (Fig. 3b), and covered with AMIC + PBC as described (Fig. 3c and d). Fig. 3e shows WBCT parasagittal reformation at 7FU showing osteoarthritis stage 1[4,25].

Table 1
Size, location and number (per case) of 238 chondral defects.

Size (cm^2) (average, range)	1.0 (0.2–6.4)
Location	
Metatarsal head dorsal (n (%))	78 (33)
Metatarsal head plantar (n (%))	54 (23)
Metatarsal head dorsal/plantar (n (%))	30 (13)
Medial sesamoid (n (%))	56 (24)
Lateral sesamoid (n (%))	16 (7)
Phalanx (n (%))	4 (2)
Number of defects	
1 (n (%))	131 (74)
2 (n (%))	31 (18)
3 (n (%))	11 (6)
4 or more (n (%))	3 (2)
in total (n)	238

Table 2
Additional procedures performed during initial surgery and later revision surgery of n = 159 patients that completed 7FU).

Additional procedure during initial surgery	**n (%)**
Synovectomy	159 (100)
Debridement / tenolysis Extensor et flexor hallucis longus et brevis, Abductor/adductor hallucis	159 (100)
Cheilectomy (limited)	159 (100)
Corrective osteotomy 1st metatarsal	126 (79)
Corrective osteotomy 1st phalanx	2 (1)
Arthrodesis 1st tarsometatarsal joint	4 (3)
Corrective osteotomy 2nd - 5th metatarsal	97 (61)
Correction arthrodesis PIP 2–3	97 (61)
Autologous cancellous bone transplantation (under MAST)	10 (6)
Revisions	
Joint-preserving surgery	20 (13)
Including AMIC+PBC	4 (3)
MTP1 fusion	0
MTP1 joint replacement	0

Patient-based analysis. Multiple procedures possible. MTP1, 1st tarso-phalangeal joint. PIP, proximal interphalangeal joint.

AMIC+PBC as part of a complex surgical approach allow for stable and favourable results after 2FU at until 7FU. No AMIC+PBC related adverse effects have been registered. The comparison with earlier published 4–7-year results of MAST confirms equivalency of MAST and AMIC+PBC at 5FU/7FU[18]. Again, using BMAC or PBC showed no influence on 2FU/5FU[2,4]. Until 7FU, the use of BMAC and PBC as adjunct might not have an effect on the tissue development and/or the clinical outcome[4,19]. Possibly, AMIC alone (without BMAC or PBC) would allow for the same results[2,4]. Again, we tried to find comparable results from the literature[2,4]. We found only the same publication with 19 patients with Hallux rigidus without deformity as two years ago[4,26]. Range of motion and scores like Functional Foot Index improved preoperatively to 1-year follow-up[26]. We still are not aware of study including AMIC whatever kind (± PBC or MAST) with Hallux valgus and with corrective osteotomies[4]. Artioli et al. recently published a review focused on osteochondral lesions of the first metatarsophalangeal joint[3]. This review is focused on osteochondral lesions and lacks inclusion of all available studies with scaffold as for example AMIC[3]. Furthermore, not a single study with validated outcome score was included[3]. The follow-up parameters did not significantly differ between 2FU, 5FU and 7FU including patient reported outcome measures (VAS FA / EFAS Score) (Table 3). The highest scores and lowest degree of osteoarthritis occurred at all FU in the groups without correction (Table 3). In comparison with the main defect location at the dorsal part of the metatarsal head in cases without deformity (comparable to Hallux rigidus), we found a lot of defects at the plantar part of the metatarsal head and the sesamoids in cases with deformity (Hallux valgus)[1,4,18]. Furthermore, we found chondral defects at the sesamoids without chondral defect at the opposite surface of the metatarsal and vice versa (so called "kissing-lesions")[4].

4.1. *Limitations[4]*

Limitations of the study are the same as discussed before because this is an ongoing longitudinal study design: subjective indication for treatment, unclear influence of associated procedures, missing control group. limited follow-up rate and missing outcome parameter for the created tissue[2,4]. The indication for AMIC+PBC was subjectively made by the surgeon[2,4]. This is the typical decision-

Table 3
Follow-up parameter.

	2FU	5FU	7FU	ANOVA (p)
Overall				
n	176	164	159	
VAS FA (average, range)	74.1 (19.1–100)	75.0 (2013–100)	73.8 (20.1–100)	0.45
EFAS Score (average, range)	17.1 (11–24)	17.3 (11–24)	17.5 (10–24)	0.56
Degree osteoarthritis (average, range)	0.8 (0–3)	0.9 (0–3)	1.0 (0–3)	0.69
Without correction				
n	37	34	32	
VAS FA (average, range)	83.2 (15.6–100)	84.2 (16.5–100)	81.9 (16.1–100)	0.76
EFAS Score (average, range)	18.8 (14–24)	19.0 (12–24)	19.1 (11–24)	0.75
Degree osteoarthritis (average, range)	0.5 (0–3)	0.6 (0–3)	0.7 (0–3)	0.67
Including Hallux valgus correction				
n	32	29	27	
VAS FA (average, range)	73.2(18.2–100)	74.2 (18.4–100)	72.5 (18.1–100)	0.58
EFAS Score (average, range)	17.5 (12–24)	17.6 (12–24)	17.2 (10–24)	0.67
Degree osteoarthritis (average, range)	0.9 (0–3)	0.9 (0–3)	1.0 (0–3)	0.87
Including Hallux valgus and lesser ray correction				
n	107	101	100	
VAS FA (average, range)	71.2 (19.1–92.3)	72.1 (15.4–98.3)	70.9 (14.5–100)	0.69
EFAS Score (average, range)	16.4 (11–24)	16.6 (10–24)	16.2 (10–24)	0.81
Degree osteoarthritis (average, range)	1.0 (0–3)	1.1 (0–3)	1.2 (0–4)	0.79

2FU/5FU/7FU, 2-/5-/7-year follow-up

making process also in other studies but does still not follow objective parameters[2,4]. We still believe that "surgical" decision-making is still better than indication based on any kind of imaging-based staging with the described limitations[2,4]. The indication for AMIC+PBC was not similar to the indication for surgery as such which was based on clinical symptoms and radiographic findings [2,4]. The simultaneous additional procedures may confound the results (Table 2). The additional procedures were considered to be necessary to restore joint function (for example corrective osteotomies of the first metatarsal in 79 %[4]. Other procedures were performed on a regular basis as for example synovectomy. Performing AMIC+PBC as single procedure would probably allow for a much more specific study results and conclusions[2]. However, we did not notice a single patient with just a chondral defect and no other pathologies[2,4]. Based on our experience and considering the literature, we still doubt that isolated chondral defects are common [2,4]. We still consider Hallux valgus deformity with de-orientation of the metatarsal head in relation to the sesamoids with increased localized joint load as a cause for the chondral defects[2,4]. Following this principle, treatment of the chondral defect alone without treating the deformity as cause would be inadequate[2,4]. In contrast, our treatment concept was and is still to address all pathologies in addition to the chondral defect[2]. If we would exclude all patients with deformities from the study, we would exclude 80 % of our patients[2,4]. This would result in a study cohort that does not reflect the real situation at least in our institution[2,4]. In addition, we have analysed cases without deformity and consequently with less procedures besides AMIC+PBC[1,4,18]. Still, we were not able to attribute the improvements solely the AMIC+PBC intervention. The same is true for the effect of different patient age, sex, height, weight, activity level, occupation and other factors. We are planning a comparative study including patients that opted out AMIC+PBC and received just microfracturing. The case number of these patients currently is too low for comparison. Another task is fixation of the matrix in the chondral defect without fibrin-glue to reduce cost, complexity and risk of infection since fibrin-glue is an allologous blood product[2,4]. We are still working on different fixation possibilities beyond suture and glue. Magnetic Resonance Imaging (MRI) was not involved in the standard treatment and therefore also not in the study[4]. At and around the authors´ institution only MRI devices with physical resolution of 2 mm for the forefoot region are available [4]. Facing the fact that the cartilage thickness in MTP1 is 1–2 mm, MRI was not considered as valuable diagnostics for MTP1 cartilage [2,4]. The follow-up rate of 80 % after 7 years is not optimal but fulfils scientific requirements and is better than all other published studies[26].

In conclusion, AMIC+PBC as treatment for chondral defects at MTP1 as part of joint preserving surgery led to improved and high validated outcome scores at 7FU. The lack of significant differences between 2-year (2FU), 5-year (5FU), and 7-year (7FU) outcomes suggests plateaued benefits.

Declaration of Competing Interest

None of the authors or the authors´ institution received funding in relation to this study. Martinus Richter is consultant of Curvebeam AI, Geistlich, Intercus and Implants International, shareholder of Curvebeam AI and proprietor of R-Innovation.

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