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Autologous matrix induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects of the first metatarsophalangeal joint - 5-year follow-up

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ABSTRACT

Background: The aim of the study was to assess the 5-year-follow-up (5FU) 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 July 17, 2016 to May 31, 2017 were included. Size and location of the chondral lesions, the Visual-Analogue-Scale Foot and Ankle (VAS FA) and the EFAS Score before treatment and at 5FU were analysed and compared with previous 2-year-follow-up (2FU). 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 238 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 (33 %), and in most patients one defect was registered (74 %). Corrective osteotomy of the first metatarsal was performed in 79 %. 176 (89 %)/164 (83 %) patients completed 2FU/5FU. VAS FA/EFAS Score were preoperatively 46.8/11.9 and improved to 74.1/17.1 at 2FU and 75.0/17.3 at 5FU on average. No parameter significantly differed between 2FU and 5FU.

Conclusions: AMIC+PBC as treatment for chondral defects at MTP1 as part of joint preserving surgery led to improved and high validated outcome scores at 2FU and 5FU. The results between 2FU and 5FU did not differ.

1. Introduction

The optimal treatment for chondral defects at foot and ankle including the first metatarsophalangeal joint (MTP1) is debatable [1,2]. 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) [3–13]. MAST showed good redults up to 7-year follow-up [1,14]. 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 [2,5,15]. Consequently, MAST and all other procedures including BMAC were not "subject to disclosure" as before but "subject to authorization" [2,15]. Therefore, the authors´ institution was not authorized to perform MAST after July 16, 2016 [2,15]. Consequently, the method was changed by replacing BMAC as part of MAST to Peripheral Blood Concentrate (PBC) resulting in AMIC+PBC [2,15]. The effect of replacing MAST (including BMAC) by AMIC+PBC was unclear and a study was conducted to compare MAST with AMIC+PBC [2,15]. 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]. Longer follow-up was considered to be important [2]. Therefore, the initial study

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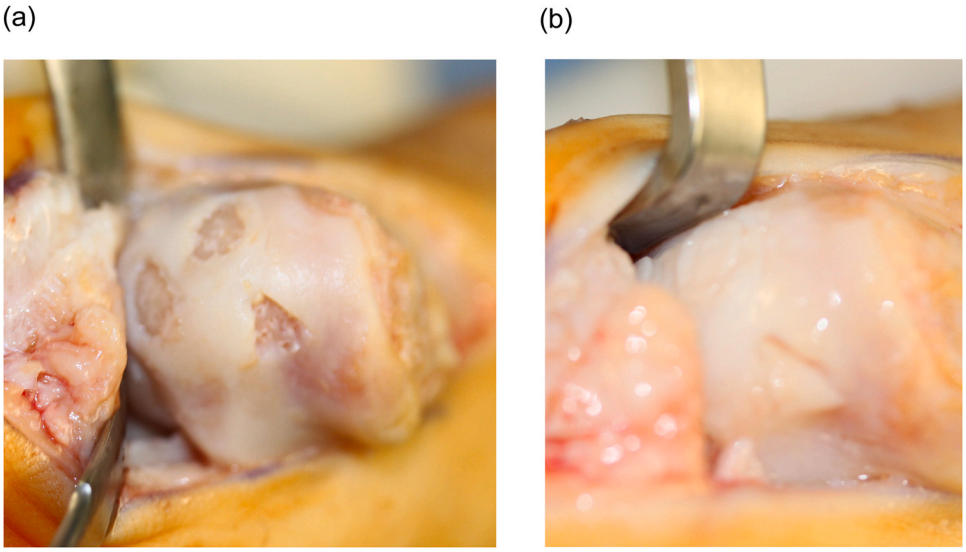

Fig. 1. a–b. Three chondral defects at the first metatarsal head (a). One defect was specified as dorsally located, size 1.0 cm × 0.7 cm (1.7 cm^2); one as plantarly located, size 0.7 cm × 0.7 cm (0.5 cm^2); one as dorsally and plantarly located, size 0.9 cm × 0.6 cm (0.5 cm^2); (a). Fig. 2a shows the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

cohort was followed until 5-year follow-up (5FU). The aim of this study was to assess the 5FU of AMIC+PBC and comparison with earlier 2FU.

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 July 17, 2016 to May 31, 2017 were included.

2.1. Inclusion criterion

The only inclusion criterion was AMIC+PBC at MTP1. 230 patients were eligible for inclusion.

2.1.1. Exclusion criteria

Exclusion criteria were bilateral treatment (n = 32 patients (14 %)), incomplete 2FU (n = 22 patients (11 %)) and revision including arthrodesis/total joint replacement of MTP1 (n = 6/2 patients (3 %/1 %)). Patients with revisions including joint preserving procedures were not excluded. No other exclusion criteria were defined.

2.1.2. AMIC+PCB indication and techniques

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 (Figs. 1 and 2) [2]. The chondral defect was debrided until stable surrounding cartilage was present. Subchondral cysts were cleared out (Fig. 2b) [1,14]. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone, and at the ground of subchondral bone defects [16]. Bone defects of more than 3 mm depth (cysts and others) were filled with autologous cancellous bone harvested locally from the resected bone (Fig. 2c). 15cc peripheral venous blood was harvested with a special syringe (Arthrex-ACP, Arthrex, Naples, FL, USA) [2]. The syringe was centrifuged (10 min, 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) [2,17–19]. 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 [2,19]. 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 [2,17]. 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 3 min (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 3 mm over this limit [2]. The impregnated matrix was fixed into the chondral lesion with fibrin glue (Tissucoll or Tisseel, Baxter, Deerfield, IL, USA) (Figures 1b and 2d) [2]. The matrix fixation was tested by moving the joint several times [2]. Adequate fixation was approved when the matrix stayed in place in the chondral lesion [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 3 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, 3, 12 months and then yearly.

2.2. Follow-up

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

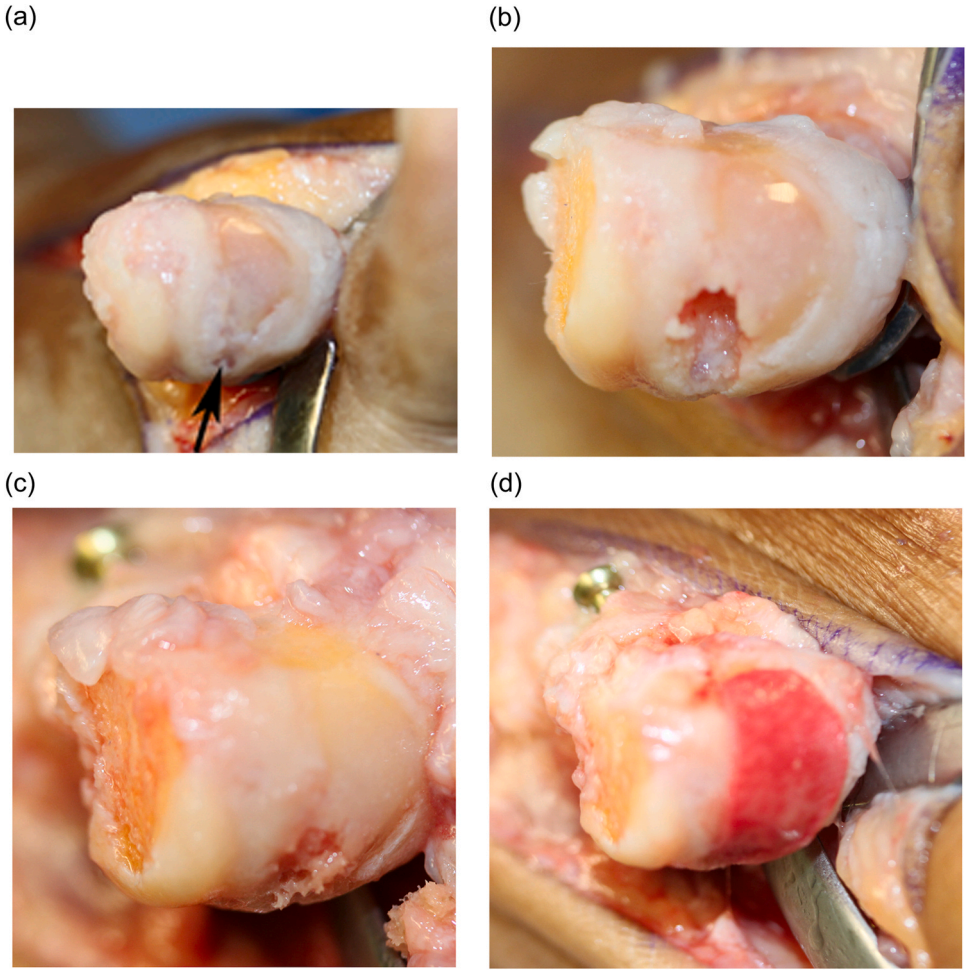

Fig. 2. a–d. Chondral defect at the first metatarsal head (a). The defect was specified as dorsally and plantarly located, size 3.2 cm × 1.1 cm (3.5 cm^2) (a). A subchondral cyst was detected (black arrow) (a). (b) shows the status after resection of the medial pseudo-exostosis, limited cheilectomy, debridement of the chondral defect and the subchondral cyst. (c) shows the status after filling of the subchondral cyst with autologous cancellous bone, microfracturing and distal metatarsal corrective osteotomy. (d) shows the matrix in place.

2.2.1. Assessment

Before surgery and at follow-ups, radiographs (bilateral views (dorsoplantar and lateral) with full weight bearing and/or Weightbearing Computed Tomography (WBCT) scans were obtained (Fig. 3a–d) [2]. Visual Analogue Scale Foot and Ankle (VAS FA) and EFAS Score were registered [20,21]. 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 [20]. 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 [14]. The degree of osteoarthritis was classified in four degrees [22]. Complications and treatment failure were registered.

2.3. 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. 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

Table 1 shows the demographic parameter, preoperative VAS FA and EFAS Score. In 21 %, no deformities were registered and considered to be corrected (Table 1). The average degree of osteoarthritis was 2.2. Table 2 shows size, location and number of the chondral defects. The chondral defect size was 1.0 cm^2 on average. The most common location was dorsal metatarsal head (33 %), and in 74 % one defect was registered. Table 3 shows the additional surgical procedures. Corrective osteotomy of the first metatarsal was performed in 79 %. 23 (13 %) patients were revised with joint-preserving surgery including joint debridement and implant removal, and 5 (3 %) including another AMIC+PBC until 2FU. No further revisions were registered after 2FU until 5FU (Table 3). No AMIC+PBC related adverse effects have been registered.

3.1. Follow-up

176 (89 %)/164 (83 %) patients completed 2FU/5FU. Table 4 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.

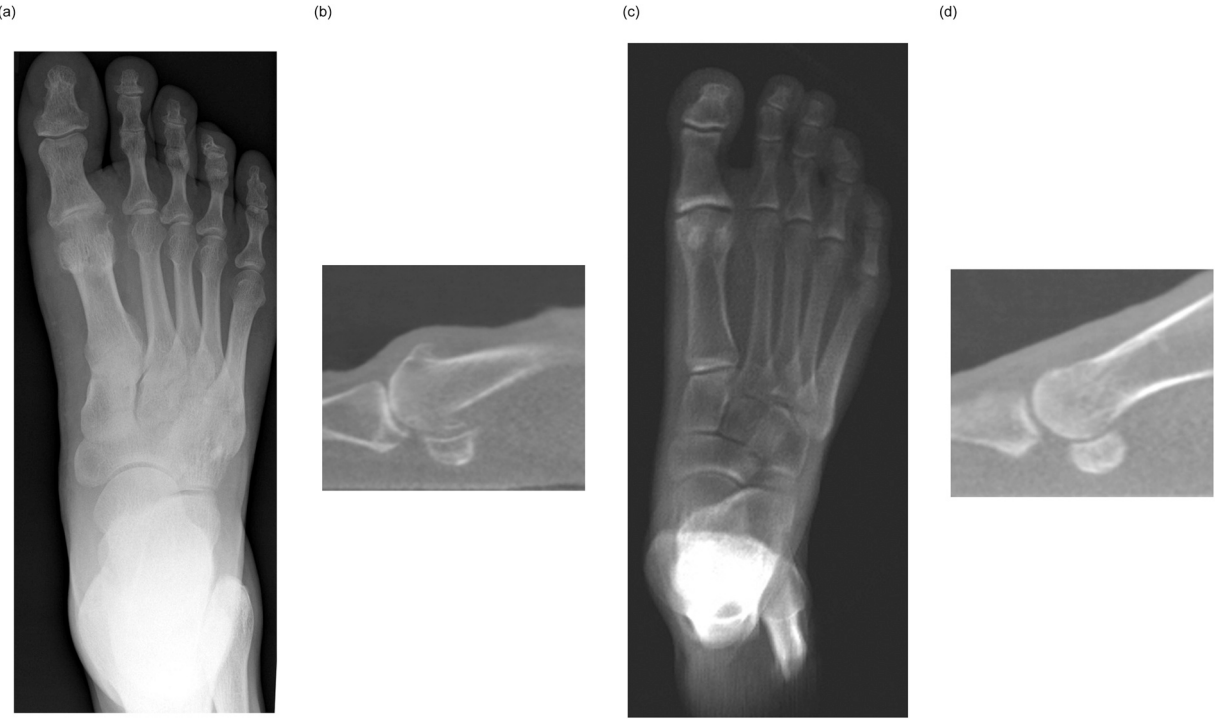

Fig. 3. a–d. Same case a Fig. 1 a–d. Preoperative dorsoplantar radiograph with weightbearing (a) and WBCT parasagittal reformation (b) showing osteoarthritis stage 3. Dorsoplantar radiograph with weightbearing (c) and WBCT parasagittal reformation (d) at 5FU showing osteoarthritis stage 1 [22].

Table 1
Demographic parameter, preoperative VAS FA and EFAS Score, and concomitant forefoot pathology.

Age (average (range))	52.6 (13–78)
Gender (male; n (%))	28 (16)
VAS FA (average (range))	46.8 (8.7–79.8)
EFAS Score (average (range))*	11.9 (2–22)
Concomitant pathology	
No deformity (n (%))	37 (21)
Hallux valgus (HV) only (n (%))	32 (18)
HV plus lesser ray deformity (n (%))	107 (61)
Degree osteoarthritis (average (range))	2.2 (1–4)

VAS FA, Visual Analogue Scale Foot and Ankle; EFAS Score, European Foot and Ankle Society Score.

Table 2
Size, location and number (per case) of chondral defects.

Size (cm^2) (average, range)	1.0 (0.2–6.4)
Location	
Metatatarsal head dorsal (n (%))	78 (33)
Metatatarsal head plantar (n (%))	54 (23)
Metatatarsal 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

3.2. Comparison 2FU with 5FU

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

Table 3
Additional procedures performed during initial surgery and later revision surgery (Patients with completed follow-up).

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

Case (patient) based analysis. Multiple procedures possible. MTP1, 1st tarso-phalangeal joint. PIP, proximal interphalangeal joint.

4. Discussion

This is the first study analysing 5FU 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]. The follow-up parameters did not significantly differ between 2FU and 5FU (Tables 2 and 3). AMIC+PBC as part of a complex surgical approach allow for stable and favorable results after 2FU until 5FU. 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 around 5FU [14]. Consequently, the main difference of both procedures, i.e. using BMAC or PBC has no influence on 2FU/5FU [2]. What does this mean? The use of BMAC and PBC as adjunct might not have an effect on the tissue

Table 4
Follow-up parameter.

	2FU	5FU	test, p
Overall			
n	176	164	
VAS FA (average, range)	74.1 (19.1–100)	75.0 (20,3–100)	t-test, 0.41
EFAS Score (average, range)*	17.1 (11–24)	17,3 (11–24)	t-test, 0.52
Degree osteoarthritis (average, range)	0.8 (0–3)	0.9 (0–3)	Chi2, 0.68
Without correction			
n	37	34	
VAS FA (average, range)	83.2 (15.6–100)	84.2 (16.5–100)	t-test, 0.73
EFAS Score (average, range)*	18.8 (14–24)	19,0 (12–24)	t-test, 0.72
Degree osteoarthritis (average, range)	0.5 (0–3)	0.6 (0–3)	Chi2, 0.69
Including Hallux valgus correction			
n	32	29	
VAS FA (average, range)	73.2(18.2–100)	74.2 (18.4–100)	t-test, 0.56
EFAS Score (average, range)*	17.5 (12–24)	17.6 (12–24)	t-test, 0.65
Degree osteoarthritis (average, range)	0.9 (0–3)	0.9 (0–3)	Chi2, 0.87
Including Hallux valgus and lesser ray correction			
n	107	101	
VAS FA (average, range)	71.2 (19.1–92.3)	72.1 (15.4–98.3)	t-test, 0.67
EFAS Score (average, range)*	16.4 (11–24)	16.6 (10–24)	t-test, 0.78
Degree osteoarthritis (average, range)	1.0 (0–3)	1.1 (0–3)	Chi2, 0.76

2FU, 2-year follow-up; 5FU, 5-year follow-up.

development and/or the clinical outcome [16]. If so, AMIC alone (without BMAC or PBC) would allow for the same results [2]. As we did not perform AMIC without PBC, we tried to find comparable results from the literature [2]. We found only one publication with 19 patients with Hallux rigidus without deformity [23]. Range of motion and scores like Functional Foot Index improved preoperatively to 1-year follow-up [23]. We are not aware of study including AMIC whatever kind (± PBC or MAST) with Hallux valgus and with corrective osteotomies. We did not consider studies with synthetic implants because the contradictious concept without cartilage restoration replacement [24]. Our follow-up parameters did also not differ between 2FU and 5FU (Table 4). The highest scores and lowest degree of osteoarthritis occurred in the groups without correction (Table 4). 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) [1,14]. 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"). We used BMAC before PBC to allow for a high concentration of mesenchymal stem cells [2,15,16,25]. The concentration of mesenchymal stem cells in PBC in comparison with BMAC is questionable [2]. We did not investigate the content of BMAC or PBC cytologically and cannot answer this question [2,15]. Another potential effect could be chemo tactical "attraction" of mesenchymal stem cell from PBC as described for PRP [2,19]. This is all unclear and debatable [2].

4.1. Limitations

Limitations of the study are: uncomplete follow-up, subjective indication for treatment, unclear influence of associated procedures, missing control group, missing outcome parameter for the created tissue, and missing control group. The indication for AMIC+PBC was subjectively made by the surgeon [2]. This is the typical decision-making process also in other studies but does still not follow objective parameters [2]. We believe that "surgical" decision-making is still better than indication based on any kind of imaging-based staging with the described limitations [2]. 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]. The simultaneous additional procedures may confound the results (Table 3). The additional procedures were considered to be necessary to restore joint function (for example corrective osteotomies of the first metatarsal in 79 %. 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]. Based on our experience and considering the literature, we doubt that isolated chondral defects are common [2]. We 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]. Following this principle, treatment of the chondral defect alone without treating the deformity as cause would be inadequate [2]. 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]. This would result in a study cohort that does not reflect the real situation at least in our institution [2]. In addition, we have analysed cases without deformity before [1,14]. 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]. We are 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. At and around the authors´ institution only MRI devices with physical resolution of 3 mm for the forefoot region are available. Facing the fact that the cartilage thickness in MTP1 is 1–2 mm, MRI was not considered as valuable diagnostics for MTP1 cartilage [2].

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 2FU and 5FU. The results between 2FU and 5FU did not differ.

Conflict of interest

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

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