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ORIGINAL ARTICLE

A clinical feasibility study to evaluate the safety and efficacy of PEOT/PBT implants for human donor site filling during mosaicplasty

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Abstract Mosaicplasty has become a well-accepted treatment modality for articular cartilage lesions in the knee. Postoperative bleeding remains potentially concerning. This study evaluates the porous poly(ethylene oxide)terephthalate/poly(butylene terephthalate) (PEOT/PBT) implants used for donor site filling. Empty donor sites were the controls. After 9 months, MRI, macroscopical and histological analysis were carried out. Treated defects did not cause postoperative bleeding. No adverse events or inflammatory response was observed. PEOT/PBT implants were well integrated. Empty controls occasionally showed protrusion of repair tissue at the defect margins. Surface stiffness was minimally improved compared to controls. Existing polymer fragments indicated considerable biodegradation. Histological evaluation of the filled donor sites revealed congruent fibrocartilaginous surface repair with proteoglycan-rich domains and subchondral cancellous bone formation with interspersed fibrous tissue in all implanted sites. The PEOT/PBT implants successfully reduce donor site morbidity and postoperative bleeding after mosaicplasty.
Level of evidence II.

Keywords Cartilage · Bone remodeling · Copolymer · In vivo · Biocompatibility · Biodegradation

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Abbreviations

PA	PolyActive
PG	Proteoglycan
DMMB	Dimethylmethylene blue staining
SO	Safranin O staining
Coll I	Immunohistochemical reaction for collagen type I
Coll II	Immunohistochemical reaction for collagen type II
PSR	Picrosirius red staining for collagen
OpAn	Optical anisotropy observed in polarized light microscope
ON	Immunohistochemical reaction for osteonectin
HA	Hyaluronic acid
CT	Connective tissue
coll I	Collagen type I
coll II	Collagen type II

Introduction

Mosaicplasty involves the collection of small-sized cylindrical osteochondral grafts ranging from 2.7 to 9 mm from the minimal weight-bearing border of the femoral condyles, followed by their transplantation to a preprepared recipient site. Surface congruence comprised of hyaline cartilage, and progressive fibrocartilaginous sprouting between the grafts resulting in appropriate integration has been demonstrated up to 5 years follow-up. Multicenter clinical studies revealed superior outcomes of mosaicplasty compared to subchondral abrasion, microfracture or Pridie perforations based on arthroscopic follow-up, MRI, modified HSS and Cincinnati scores. Mosaicplasty has become a valid technique for the treatment of articular cartilage lesions in the knee [1, 2].

Despite the good-to-excellent results, donor site morbidity remains concerning [2]. Donor site bleeding is particularly challenging. Sokoloff et al. showed that trivalent cations such as Fe^{3+} can cause irreversible collapse of hydrated glycosaminoglycan side chains of proteoglycan molecules which are predominantly responsible for the load bearing capacity of the hyaline cartilage [3]. Extensive in vitro studies suggest that interleukins, such as IL-1, stimulate chondrocytes to increase the production of hydrogen peroxide. In reaction with hemoglobin-derived iron, hydroxyl radicals are formed within the joint environment. These radicals irreversibly inhibit cartilage matrix synthesis by the induction of chondrocyte apoptosis [4–9]. While Jansen et al. claim a complete reversible inhibition by blood on matrix synthesis after 24 h, they also found a prolonged damage of joint cartilage already after 48 h of blood exposure to cartilage [10].

Both natural and synthetic implants have been applied in cartilage repair.

Only few studies have addressed osteochondral donor site filling. In a canine model, Feczko et al. evaluated hydroxylapatite, polycaprolactone, carbon and collagen implants [1]. Only compressed collagen showed acceptable fibrocartilaginous resurfacing. Initial mechanical properties of collagen implants, however, are substantially inferior to their synthetic counterparts.

Based on its biocompatibility, biodegradability and mechanical properties, it is suggested that porous PEOT/PBT implants are suitable candidates for donor site filling. In vitro cartilage engineering is facilitated by PEOT/PBT implants [11–13]. Preclinical studies using the rabbit femoral osteochondral defect model demonstrated surface congruent fibrocartilaginous resurfacing with robust subchondral bone formation at 12 and 52 weeks follow-up [14].

In this study, porous PEOT/PBT implants were used to fill donor sites during mosaicplasty. According to our hypothesis, PEOT/PBT implants should reduce the incidence of postoperative hemarthrosis and should promote osteochondral donor site filling. Safety and efficacy was assessed arthroscopically, histologically and with MRI scans after 9 months follow-up.

Materials and methods

PEOT/PBT implants

Elastomeric copolymer poly(ethylene oxide)terephthalate/poly(butylene terephthalate) (PEOT/PBT) was used to prepare porous implants by compression molding followed by porogen leaching [13, 15], resulting in implants with a porosity of 75%, average pore size of 182 μm and dynamic stiffness 1.7 MPa at 0.1 Hz. The specific composition of the PEOT/PBT implant is 55% PEOT and 45% PBT. The molecular weight of the poly(ethylene oxide) is 300 Da. (Compositional code: 300PEOT55PBT45.) Implant dimensions were 7.5 mm in diameter and 10 mm in length (Fig. 1a). GMP manufactured implants were sterilized with 25 kGY gamma irradiation.

Study design

The study followed an open, non-randomized, concurrent controlled, single center, clinical feasibility design. The study was approved by an independent medical ethical committee and performed in accordance with the Declaration of Helsinki [16], ICH GCP and EN540 guidelines. Informed consent was provided to all patients. Patients included in the PEOT/PBT group underwent MRI scanning within 7 days and 9 months postsurgery, and follow-up arthroscopy was performed at 9 months postsurgery for macroscopic evaluation and biopsy collection.

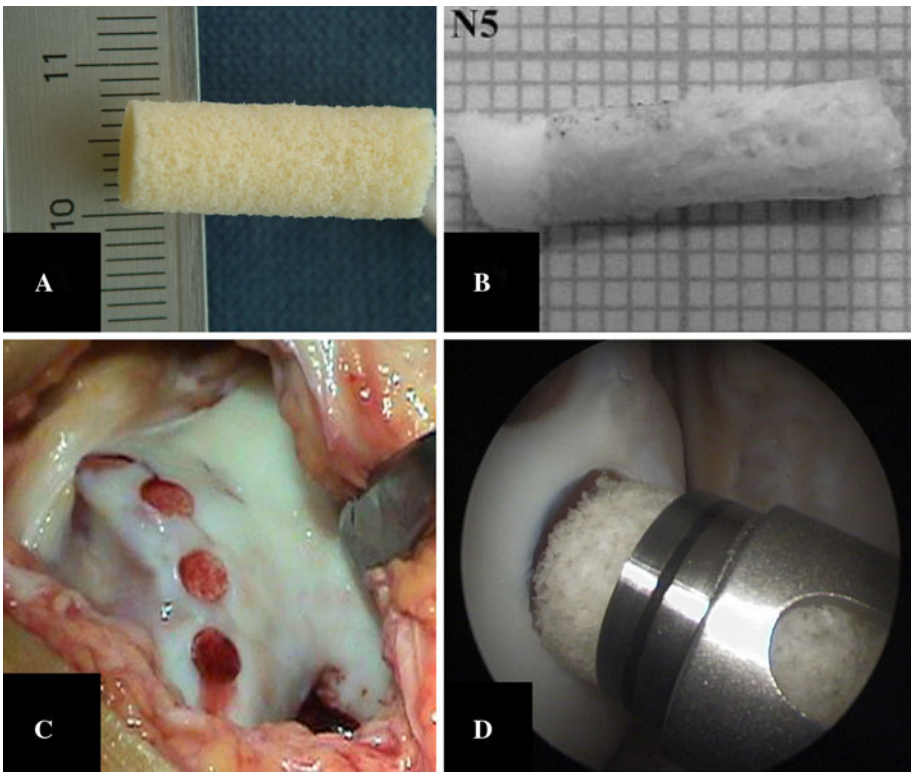

Fig. 1 Application of PEOT/PBT implants to fill donor sites during mosaicplasty. **a** PEOT/PBT plug prior to the insertion and **b** biopsy after 9 months. Insertion of PEOT/PBT during **c** an open procedure and **d** an arthroscopic procedure

Patients who met the inclusion criteria and who underwent the same procedure within the timeframe of the study but did not wish to be treated in the treatment group were included in a concurrent control group. These patients were evaluated at 24 months follow-up for clinical outcome. No additional analysis was performed in this group.

Patient inclusion criteria

All patients participating in this study met the following inclusion and exclusion criteria:

The patients were male or female aged between 18 and 55 years. They qualified for an autologous osteochondral grafting procedure for femoral condyle cartilage lesions with a maximum defect size of 4 cm^2. Instability and malalignment were exclusion criteria. Concomitant procedures (six ACL reconstructions, one HTO, one meniscus resection, one lateral release) were no exclusion criteria.

The total number of patients included in the PEOT/PBT implant treatment and control were ten and four, respectively (Table 1).

Surgical method

Both arthroscopic (8 patients, Fig. 1b) and open (2 patients, Fig. 1c) procedures were performed depending on the size and location of the lesion. During the open procedure, the femoral condyles' margins served as donor sites.

During the arthroscopic technique, the medial border of the femoral condyle was the primary donor site; 6.5-mm-wide cylindrical grafts were harvested with a 15 mm average length perpendicularly to the donor sites using a tubular chisel and harvesting tamp. PEOT/PBT implants were hydrated for 15 min in sterile saline at room temperature and implanted to the donor sites with press-fit insertion manually (open procedure) or via an adjustable plunger (arthroscopy) (Fig. 1b).

In the PEOT/PBT group, two to six scaffolds were used per patient with an average of 3.5. In the control group, the donor sites were left empty.

For postoperative pain control, intravenous (on the day of surgery) or oral pain medication was prescribed. Postoperatively, 4 weeks non-weight bearing and further 4 weeks partial weight bearing were advised. Full activities were accomplished within 3–6 months.

Evaluation and clinical analysis

Postoperative bleeding, clinical symptoms and MRI were assessed in both groups. In the PEOT/PBT group, MRI and second look arthroscopy were also used to check the surface congruency. MRI was performed preoperatively, on the 7th postoperative day, in the 3rd postoperative month and after one and 2 years. Clinical scoring systems (modified HSS, Lysholm, Cinncinnatti) were employed before the operation, 3, 9, 12 and 24 months postoperatively.

Table 1 Patient material

Patient number	Patient age/ gender	Concomitant procedures	Group	Defect size (cm^2)	Graft number	Polyactive plugs in donor sites	Hemarthros after surgery
1	31♂	ACL repair	Polyactive	0.4	2	2	No
2	41♂	No	Polyactive	2.5	5	5	No
3	43♂	Lateral meniscus resection	Polyactive	0.6	2	2	No
4	20♀	ACL repair	Polyactive	1.35	4	4	No
5	45♂	ACL repair	Polyactive	0.7	2	2	Yes, but synovial fluid was not aspired
6	44♀	Lateral release	Polyactive	2	3	3	Yes, but synovial fluid was not aspired
7	44♂	HTO	Polyactive	4	10	4	Yes, but synovial fluid was not aspired
8	38♂	ACL repair	Polyactive	2	3	3	Yes, but synovial fluid was not aspired
9	35♂	ACL repair	Polyactive	1	1	1	No
10	30♀	ACL repair	Polyactive	1.5	2	2	No
11	23♂	No	Control	3	6		20 ml synovial fluid was aspired
12	23♀	No	Control	2.5	5		15 ml synovial fluid was aspired
13	26♀	No	Control	1	1		15 ml synovial fluid was aspired
14	37♀	No	Control	1.1	2		Yes, but synovial fluid was not aspired

Table 2 Evaluation and analyses performed during the clinical feasibility study as a function of follow-up time

Evaluation	Clinical study follow-up					
	Preoperative	1–7 days	7 days	3 months	9 months	12 months
Postoperative bleeding		*				
Clinical score	*			*	*	*
MRI	*		*	*		*
Follow-up arthroscopy					*	
Histology					*	

Second look (arthroscopy) was performed 9 months postoperatively (Table 2). During the follow-up arthroscopies, biopsies were harvested for histological analysis.

All patients (10 PEOT/PBT-filled and 4 control patients) had the preoperative, 3rd, 9th, 12th and 24th month scoring and preoperative and 7th day, 3rd, 12th and 24th month postoperative MRI assessments.

Histology

For histological analyses, biopsies were fixed in Sainte-Marie's fixative [17, 18], decalcified in 10% EDTA and embedded in paraffin. Longitudinal 5–8 μm thick serial sections were stained with hematoxylin–eosin for general histology, dimethylmethylene blue (DMMB) [19] and Safranin O [20] for proteoglycans, and picosirius red for collagen (3) and evaluated using normal and polarized light microscopy [19]. Sections were also immunostained for type I and II collagens and osteonectin. For indirect immunohistochemistry, antihuman primary antibodies (AB) were used (Chemicon/Millipore, Termecula, CA, USA). Incubations were carried out with anticollagen type I monoclonal AB at 1:250 dilution overnight at 4°C, with anticollagen type II monoclonal AB at 1:25 dilution for 2 h at room temperature and with antiosteonectin polyclonal AB at 1:200 dilution overnight at 4°C. The reactions were visualized by the relevant secondary AB containing avidin-biotin-peroxydase kits (Vectastain Elite Kit, Vector Laboratories, Burlingame, CS, USA) and finally with 3,3-diaminobensidine chromogen containing H_2O_2 substrate. Hyaluronic acid (HA) was detected by using a highly specific biotinylated hyaluronon-binding probe bHABS (courtesy of R. and M. Tammi, University of Kuopio, Finland) [21].

Results

Postoperative intra-articular bleeding was absent in all treated defects. No adverse events, synovitis, hemarthrosis, arthrofibrosis or other inflammatory response were observed. The clinical outcome was not statistically different in the two groups (Table 1).

Arthroscopic assessment demonstrated surface congruency and implant integration with the host tissue after 9 months (Fig. 2a; Table 3).

The surface of the filled areas was in level with the neighboring surface, and it was similar or harder than the reparative tissue at the empty donor sites. No signs of hemosiderosis were found. MRI revealed surface congruency of all filled donor sites and indicated appropriate osteointegration of the implants (Fig. 2b, c, d). Empty controls occasionally showed protrusion of repair tissue at the defect margins. Subchondral cortical bone formation was not observed at this stage. The stiffness of the repair tissue at the surface of filled donor sites was equal or slightly improved when compared to empty controls.

By histological evaluation of the filled donor sites, formation of fibrocartilaginous surface repair was observed in 5 out of 7 biopsies (Fig. 3; Table 3). The tissue was characterized by the presence of large proteoglycan-rich areas indicated by intense metachromatic staining. Induced optical anisotropy was observed after DMMB staining reaction in polarized light microscope, suggesting the spatial orientation of proteoglycan molecules. This feature is typical for the extracellular matrix of hyaline cartilage. In two other cases, the articular surface was covered by a dense connective tissue.

Histological evaluation showed substantial fragmentation in all filled donor sites (Fig. 3a–d). This demonstrates the biodegradability of the implant. The integration of the PEOT/PBT implant and the absence of a chronic inflammatory response demonstrate the long-term biocompatibility of this polymer. The polymer fragments are frequently surrounded by a few multinucleated giant cells indicating active ongoing phagocytotic degradation. Histological analysis detected collagen-rich connective tissue, HA and trabecular bone. Type I collagen was detected in the fibrous surface and underlying connective tissue

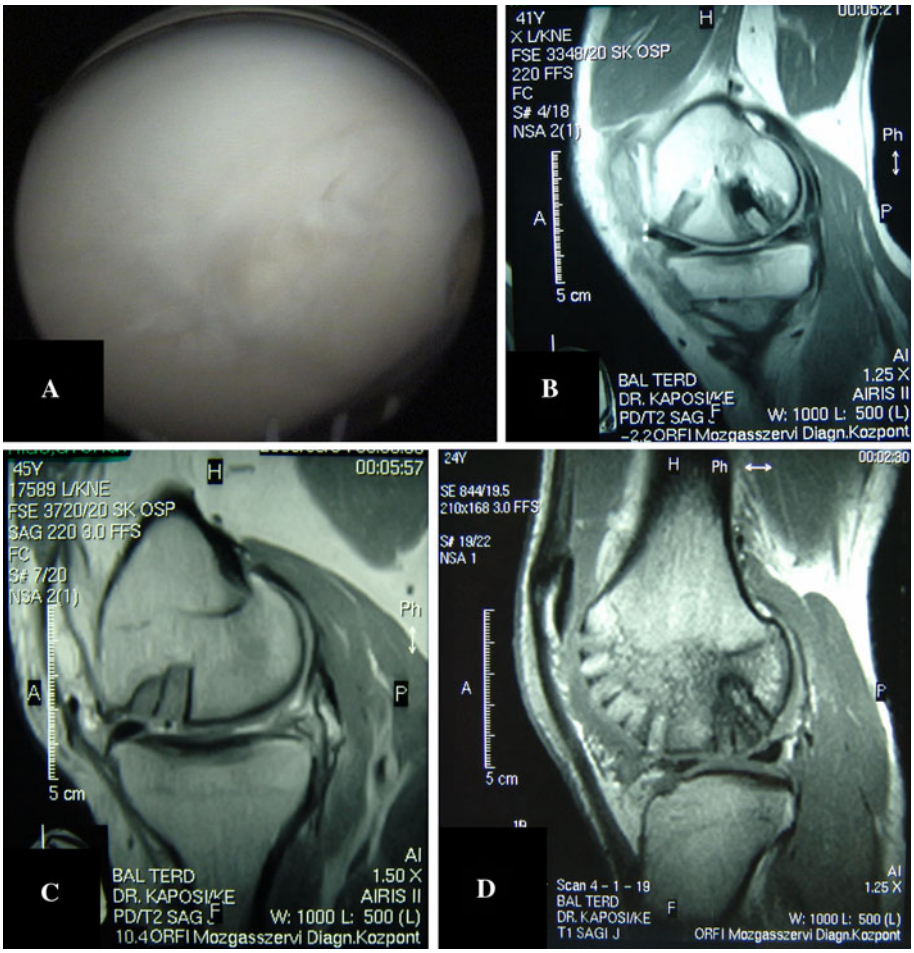

Fig. 2 Arthroscopy and MRI evaluation of the filled donor sites after 9 months. **a** Arthroscopy of the donor site. Note the surface congruency and integration with surrounding host tissue. **b** MRI showing the filled donor site (*left*) and recipient site (*right*). Donor site indicates homogenous scaffold filling and osseous integration. **c** MRI showing two filled donor sites. Note the homogenous filling. **d** MRI showing six filled donor sites and the recipient site indicating surface congruency of the filled sites and the osseous integration of the scaffolds

Table 3 Data of follow-up arthroscopies

Patient number	Age/ gender Defect size Graft no	Group	Brittberg scoring system			Biopsy	
			Degree of defect repair	Integration to border zone	Macroscopic appearance	Articular surface	Content of the donor site below the surface tissue
1	31♂ 0.4 cm^2 2 pieces	Polyactive	in level with surrounding cartilage	3/4 of graft integrated, 1/4 with a notable border >1 mm width	Intact smooth surface	Fibrocartilage containing PG and HA molecules, spatially oriented collagen I fibers and PG. Some traces of collagen II are found at the periphery of some samples	Well-developed trabecular bone with coll I fibers and osteonectin, moderate amounts of dense CT with coll I and HA. PA particles exhibiting OpAn both in stained and non-stained sections. Multinucleated giant cells are occasionally attached to the surface PA particles
2	41♂ 2.5 cm^2 5 pieces	Polyactive	No data				
3	43♂ 0.6 cm^2 2 pieces	Polyactive	in level with surrounding cartilage	3/4 of graft integrated, 1/4 with a notable border >1 mm width	Intact smooth surface	Fibrocartilage containing PG and HA molecules, spatially oriented collagen I fibers and PG. Some traces of collagen II are found at the periphery of some samples	Well-developed trabecular bone with coll I fibers and osteonectin, moderate amounts of dense CT with coll I and HA. PA particles exhibiting OpAn both in stained and non-stained sections. Multinucleated giant cells are occasionally attached to the surface PA particles
4	20♀ 1.35 cm^2 4 pieces	Polyactive	in level with surrounding cartilage	3/4 of graft integrated, 1/4 with a notable border >1 mm width	Intact smooth surface	Dense connective tissue with collagen I fibers and HA	
5	45♂ 0.7 cm^2 2 pieces	Polyactive	in level with surrounding cartilage	3/4 of graft integrated, 1/4 with a notable border >1 mm width	Intact smooth surface	Fibrocartilage containing PG and HA molecules, spatially oriented collagen I fibers and PG. Some traces of collagen II are found at the periphery of some samples	
6	44♀ 2 cm^2 3 pieces	Polyactive	No data				
7	44♂ 4 cm^2 10 pieces	Polyactive	in level with surrounding cartilage	Complete integration with surrounding cartilage, demarcating border <1 mm	Intact smooth surface	Dense connective tissue with collagen I fibers and HA	Well-developed trabecular bone with coll I fibers and osteonectin, moderate amounts of dense CT with coll I and HA. PA particles exhibiting OpAn both in stained and non-stained sections. Multinucleated giant cells are occasionally attached to the surface PA particles
8	38♂ 2 cm^2 3 pieces	Polyactive	in level with surrounding cartilage	3/4 of graft integrated, 1/4 with a notable border >1 mm width	Intact smooth surface	Fibrocartilage containing PG and HA molecules, spatially oriented collagen I fibers and PG. Some traces of collagen II are found at the periphery of some samples	

Table 3 continued

Patient number	Age/ gender Defect size Graft no	Group	Brittberg scoring system			Biopsy	
			Degree of defect repair	Integration to border zone	Macroscopic appearance	Articular surface	Content of the donor site below the surface tissue
9	35♂ 1 cm^2 1 pieces	Polyactive	No data				
10	30♀ 1.5 cm^2 2 pieces	Polyactive	in level with surrounding cartilage	Complete integration with surrounding cartilage, demarcating border <1 mm	Intact smooth surface	Fibrocartilage containing PG and HA molecules, spatially oriented collagen I fibers and PG. Some traces of collagen II are found at the periphery of some samples	Well-developed trabecular bone with coll I fibers and osteonectin, moderate amounts of dense CT with coll I and HA. PA particles exhibiting OpAn both in stained and non-stained sections. Multinucleated giant cells are occasionally attached to the surface PA particles
11	23♂ 3 cm^2 6 pieces	Control	No data				
12	23♀ 2.5 cm^2 5 pieces	Control	No data				
13	26♀ 1 cm^2 1 pieces	Control	No data				
14	37♀ 1.1 cm^2 2 pieces	Control	No data				

PG detected with DMMB and SO, showing Coll I and HA reactions. Spatially oriented collagen fibers and PG molecules were shown by OpAn after PSR and DMMB

Dense connective tissue showed Coll I and HA reactions as well as OpAn after PRS

Trabecular bone showed Coll I and ON reactions and OpAn after PSR

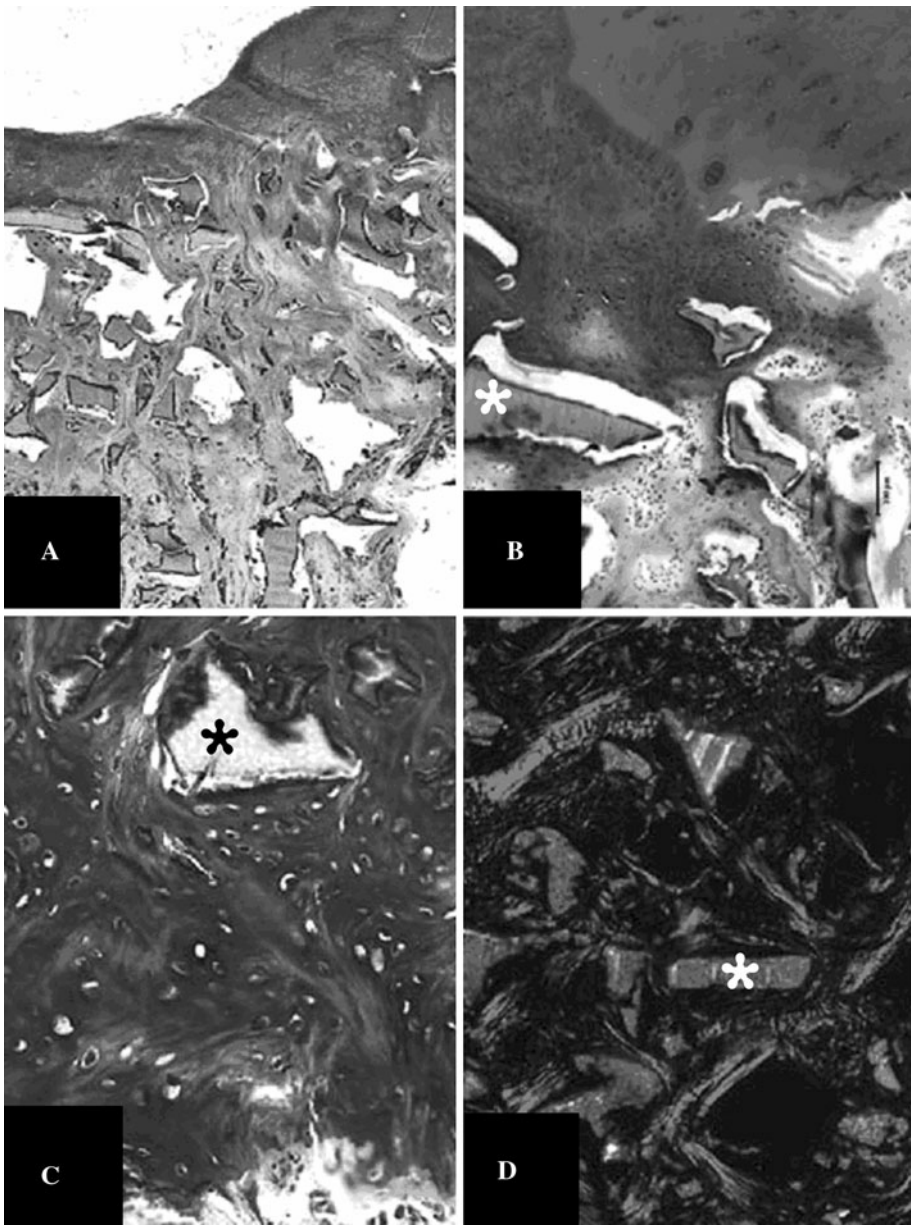

Fig. 3 Histological evaluation of biopsies after 9 months. **a** Fibrocartilage formation at the surface of PEOT/PBT. Dimethylmethylene blue staining (DMMB); magnification ×4, *bar* indicates 500 µm. **b** Intense metachromatic staining at the surface of the biopsy indicating proteoglycan-rich domains. Note the demarcation between native (*left*) and newly formed cartilage like tissue (*right*). Safranin O staining; magnification ×10, *bar* indicates 200 µm. **c** Calcified polymer fragment enclosed by fibrocartilaginous tissue. Note the absence of inflammation or foreign body responses. DMMB staining; magnification ×20, *bar* indicates 100 µm. **d** Strong optical anisotropy of collagen fibers in between residual PEOT/PBT polymer fragments. Picosirius Red staining and polarized light microscopy, magnification ×10, *bar* indicates 200 µm. *Asterisk* (*) indicates polymer fragment

(Fig. 4a). Some traces of type 2 collagen were detected by immunohistochemistry at the periphery of the implants.

Newly formed bone was found in all biopsies. Biopsies stained positively for osteonectin (Fig. 4b). The osteoconductive property of the PEOT/PBT implants was verified by the detection of osteoblasts and osteocytes.

Discussion

This study evaluated the safety and efficacy of biodegradable PEOT/PBT implants to fill donor sites during mosaicplasty. We were able to demonstrate that PEOT/PBT is a safe and biocompatible filler, which prevents postoperative bleeding, supports subchondral integration and facilitates congruent resurfacing with mainly fibrocartilaginous tissue.

Safety was demonstrated by the absence of adverse intra-articular events or implant-related complications. Long-term biocompatibility was proven by the absence of a chronic inflammatory response and the presence of a mild foreign body response. The latter is inherent to biodegradable synthetic biomaterials. Few giant cells were occasionally observed adjacent to PEOT/PBT fragments, indicating ongoing phagocytosis [22]. Fragments were mainly observed in the subchondral area.

Extrusion was not observed. Fragments occasionally revealed a clear demarcation following DMMB staining

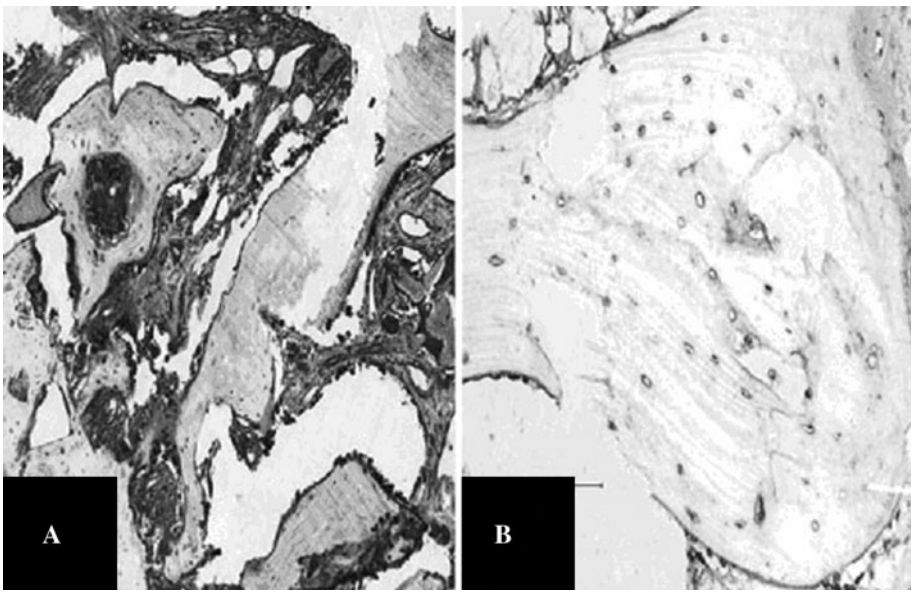

Fig. 4 Histological evaluation of biopsies after 9 months. **a** Densely packed collagen type 1 at the surface of the PEOT/PBT. Immunohistochemistry, magnification ×10, *bar* indicates 200 μm. **b** Detection of osteonectin in biopsies after 9 months indicating newly formed bone. Immunohistochemistry; magnification ×20, *bar* indicates 100 μm

reaction, indicative for polymer calcification. Calcification of PEOT/PBT has been demonstrated to be a key attribute for its bone bonding and osteoconductive character [23–26].

Hydrophobic compositions (low PEOT/PBT ratios), however, performed better in comparison with hydrophilic compositions with respect to soft tissue biocompatibility and the amount and quality of deposited soft tissue. The hydrophobic composition in this clinical trial seems to have supported appropriate biocompatibility, tissue integration and osteochondral healing.

The expected prevention of postoperative bleeding following press-fit insertion of PEOT/PBT implants can be explained by its hydrogel behavior which induces implant swelling thereby sealing the defect [27].

Good implant integration with the surrounding bone was established at the MRI and histological level. Osteolytic responses were absent. In the subchondral area, ample newly formed cancellous bone interspersed with fibrous tissue was observed. The properties of bone bridging and bone bonding by PEOT/PBT have been described in animal experiments using goats [25], beagle dogs [28] and rabbits [29]. Factors such as close contact between surrounding bone and implant material, appropriate porous and interconnected structures and the absence of micromovement, support bone ingrowths into the implant and allow good integration [30]. These critical parameters appear to be provided by the press-fit insertion and physical–chemical and structural properties of the PEOT/PBT implants and facilitate osteoconduction.

The postoperative behavior of empty donor sites after mosaicplasty has already been evaluated in previous experimental studies [1, 2]. These evaluations showed that fibrous or cancellous bone filling occurs, and natural healing processes result in mainly fibrous or fibrocartilaginous tissue resurfacing of the defects, providing an acceptable gliding surface in these limited weight-bearing areas. This healing process, however, takes approximately 8–10 weeks, and complications such as postoperative bleeding and donor side morbidity during this period have been reported [31].

The PEOT/PBT implants supported and favored fibrocartilage rather than fibrous tissue formation at the surface. The absence of fissures indicated an appropriate integration of the newly formed tissue with cartilage host tissue. Surface fibrillation, for example, was occasionally observed in control defects.

Although the increased cellular density indicates its reparative nature, the presence of several intense metachromatically stained hyaline-like areas in the implant filled defects is worth mentioning.

Bone marrow-derived progenitor cells play a key role in the osteochondral repair process. The PEOT/PBT implants likely provided the appropriate microenvironment for the attachment proliferation and differentiation of these cells, thereby enabling fibrocartilaginous tissue formation and subchondral bone remodeling [32, 33]. It has been shown that PEOT/PBT copolymers can support the culture of fibroblasts [34], chondrocytes [35], bone and mesenchymal stem cells [23–27, 36, 37]. In addition, conditions such as high cell density, condensation and the low oxygen concentration may occur, which all favor the chondrogenic differentiation of mesenchymal stem cells [38–42].

The mechanical properties of the filling material are also essential factors which allow cartilage formation in the defect site. Although the donor sites are located at limited weight-bearing areas, studies have indicated that there is a relationship between a defect and mechanically induced

degeneration [43–46]. Reduction in local stress concentrations around defects favors cartilage repair [47]. Results suggest that donor site filling reduces local stress.

The filling material can withstand the forces and even stimulate cartilage like qualities [48, 49]. The PEOT/PBT composition and porous matrix morphology used for osteochondral defect filling have been tailored to establish mechanical properties compliant with native cartilage [48–50].

Due to the small number of patients involved in this study, further investigation is required regarding the long-term characteristics of the PEOT/PTB implants.

Conclusion

This study demonstrates the safety, long-term biocompatibility and osteoconductivity of porous PEOT/PBT implants. The ease of arthroscopic scaffold insertion, the congruent surface tissue repair of predominantly fibrocartilaginous nature and the absence of intra-articular adverse events indicate its suitability for donor sites filling during mosaicplasty to prevent postoperative bleeding and donor site morbidity.

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Conflict of interest We wish to draw the attention of the Editor to the following facts, which may be considered as potential conflicts of interest and to significant financial contributions to this work. The clinical feasibility study presented in this manuscript has been sponsored by the company IsoTis OrthoBiologics. IsoTis OrthoBiologics is not pursuing product development activities related to PolyActive and cartilage repair. CellCoTec did not sponsor the clinical feasibility study, but is pursuing product development activities related to the use of PolyActive in (osteo)chondral cartilage defects.

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