EXPERIMENTAL STUDY

Evaluation of subsidence, chondrocyte survival and graft incorporation following autologous osteochondral transplantation

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Abstract

Purpose   The aim of this study was to evaluate subsidence tendency, surface congruency, chondrocyte survival and plug incorporation after osteochondral transplantation in an animal model. The potential benefit of precise seating of the transplanted osteochondral plug on the recipient subchondral host bone ('bottoming') on these parameters was assessed in particular.

Methods   In 18 goats, two osteochondral autografts were harvested from the trochlea of the ipsilateral knee joint and inserted press-fit in a standardized articular cartilage defect in the medial femoral condyle. In half of the goats, the transplanted plugs were matched exactly to the depth of the recipient hole (bottomed plugs; $n = 9$), whereas in the other half of the goats, a gap of 2 mm was left between the plugs and the recipient bottom (unbottomed plugs; $n = 9$). After 6 weeks, all transplants were evaluated on gross morphology, subsidence, histology, and chondrocyte vitality.

Results   The macroscopic morphology scored significantly higher for surface congruency in bottomed plugs as compared to unbottomed reconstructions ($P = 0.04$). However, no differences in histological subsidence scoring between bottomed and unbottomed plugs were found. The transplanted articular cartilage of both bottomed and unbottomed plugs was vital. Only at the edges some matrix destaining, chondrocyte death and cluster formation was observed. At the subchondral bone level, active remodeling occurred, whereas integration at the cartilaginous surface of the osteochondral plugs failed to occur. Subchondral cysts were found in both groups.

Conclusions   In this animal model, subsidence tendency was significantly lower after 'bottomed' versus 'unbottomed' osteochondral transplants on gross appearance, whereas for histological scoring no significant differences were encountered. Since the clinical outcome may be negatively influenced by subsidence, the use of 'bottomed' grafts is recommended for osteochondral transplantation in patients.

Keywords   Autologous osteochondral transplantation ·
Osteochondral defect · Cartilage repair · Cartilage defect ·
Histology

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Introduction

Cartilage repair is a major topic in orthopedic surgery. Even relatively small cartilage lesions frequently induce pain and disability for the patient. Without repair, small lesions may even progress to larger, more generalized arthritic lesions [21]. Commonly advocated repair techniques for these smaller lesions are microfracture, autologous chondrocyte implantation (ACI), and autologous osteochondral transplantation (AOT) [2, 28]. Compared with ACI, the advantage of AOT is that it is a one-stage procedure and mature hyaline cartilage is present in the defect site directly after transplantation.
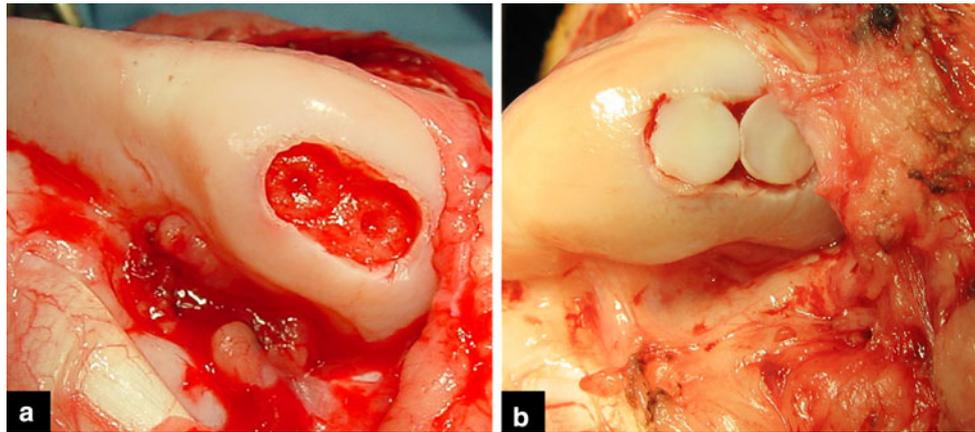
Fig. 1 **a** Standardized 3-mm-deep oval defect on the medial femoral condyle (length 12 mm, width 6 mm). **b** Final result of a two-plug osteochondral transplantation on the medial femoral condyle

In literature both very positive reports [7–9, 13, 14] and concerns [1, 18] have been presented for AOT in the knee. Concerns are related to donor site morbidity [6, 24, 27], to survival of the transplanted cartilage [5, 11, 26], and to the reported negative outcome in some patient series [3, 18]. Particularly mal-indications, treatment of too large defects, the use of too large plugs or co-morbidity within the knee could all negatively influence the clinical outcome of AOT [1, 18].

Adequate positioning, together with intrinsic stability of the transplanted plugs are likely to be important prerequisites to reach clinical success. Both are important for adequate osseous integration of the transplanted plug in the subchondral bone and for survival of the hyaline cartilage [20, 23]. In addition, osteochondral transplants should be placed flush with the joint surface, since leaving the plugs proud generates stresses at the edges leading to early damage to the graft [19, 23, 29]. Subsidence of plugs, on the other hand, leads to stresses at the rim of the host cartilage [10, 15, 16], with similar damage there.

Earlier biomechanical studies on an AOT cadaver model, using the OATS® system, reported on relatively high forces needed to displace 'bottomed' plugs beyond flush level as compared to plugs placed with a gap between the cylinder graft and the bottom of the recipient subchondral bone defect ('unbottomed' plugs). From this biomechanical study, well-seated ('bottomed') osteochondral plugs thus seemed less susceptible for subsidence [16, 17].

The aim of this goat study was to compare bottomed versus unbottomed osteochondral transplants in vivo. It was hypothesized that bottomed plugs would indeed be superior in maintaining their flush level and by that would lead to a better gross morphology of the reconstruction and to a better survival of hyaline cartilage of both donor and host cartilage at a follow-up period of 6 weeks.

Materials and methods

Eighteen female goats were operated on the right knee joint under general anesthesia. Prior to surgery, each goat had been randomly assigned to receive two bottomed or unbottomed plugs. Centrally, in the weight-bearing area of the medial femoral condyle, a standardized oval defect (length 12 mm, width 6 mm) of 3 mm depth was created in an AP orientation with the use of a customized drill guide, a circular drill of 6 mm diameter and a small sharp osteotome (recipient site) (Fig. 1a). In accordance with clinical practice, a cylindrical osteochondral transplantation was performed to restore the articular defect using a 6 mm diameter osteochondral autograft transfer system (OATS®; Arthrex, St. Anthonis, The Netherlands).

Two donor osteochondral plugs were harvested from the lateral trochlea of the goat knee, which is in accordance with the situation in patients [25]. Care was taken to harvest plugs as much perpendicular to the articular surface as possible without penetrating the lateral wall of the trochlear groove. The harvested donor plugs were adjusted to an exact length of 8 mm, measured with a precision slide calliper, by removal of some deep trabecular bone by a surgical bone nibbling plier.

The recipient site was restored using the two available donor plugs from the trochlea. Depending on the assigned treatment, a recipient hole with an 8 or 10 mm depth was created in the femoral condyle defect for a bottomed or unbottomed situation, respectively. The precise depth was verified with a vernier calliper. The bottom of the recipient hole was softly tampered, with the provided steel rod, to flatten it in order to ensure an exact matching depth and direct contact of the transplanted plug on the bottom of the recipient hole in case of a bottomed transplantation. Subsequently, the available donor osteochondral plug was gently tampered into place until flush level with the

adjacent articular cartilage was obtained. After the first plug was in place, the entire procedure was repeated for the second transplant (Fig. 1b). As a result in the bottomed situation, plugs were seated exactly on the flattened bottom, and in the unbottomed situation, the plugs were floating 2 mm above the flattened bottom.

The trochlear donor site defects were either left empty in six goats or were filled with impacted remainders of the available subchondral bone derived from preparing the recipient holes, leaving small, but shallow defects (12 goats). In six of these 12 goats, the remaining shallow defects were completely filled up to a flush level with a commercially available hemostatic collagen type I sponge (Spongostan™; Ferrosan A/S, Soeborg, Denmark). It was hypothesized that partly restoring the donor defect with the available impacted subchondral bone would lead to a better healing of these defects as compared to empty defects. In addition, filling the remaining defect with a collagen type I sponge would then possibly further enhance the healing process of the donor defect.

Directly after surgery, the goats were placed in a hammock for 7 days. The first 3 days the goats received standard injections of flunixine (1 mg/kg) (Finadyne®; Schering-Plough Animal Health, Oss, The Netherlands) and buprenorphine (0.018 ml/kg) (Temgesic®; MSD Animal Health, Oss, The Netherlands) as analgesic. Antibiotic prophylaxis consisted of ampicillin subcutaneously administered for 5 days postoperatively (7.5 ml/day) (Albupen®; Intervet, Boxmeer, The Netherlands). After 7 days, the goats were transported in the hammock to an outdoor farm where they were allowed to move freely and unrestricted.

All goats received one injection of three different fluorochromes. After 2 weeks, tetracycline (25 mg/kg) was administered, after 4 weeks calcein green (25 mg/kg) and finally after 6 weeks, 2 days before killing, alizarin red (30 mg/kg). After 6 weeks, the goats were killed with an overdose of pentobarbital (Nembutal®, CEVA Santé Animale, Maassluis, The Netherlands) and the knee joint was completely dissected from femur en tibia. All investigations were conducted in conformity with ethical principles of research and all protocols were approved by the institutional Animal Ethics Committee (RU-DEC2007-106).

Macroscopic scoring

Directly after harvesting, the knee joint was opened and photographs of the recipient and donor sites were taken. The photographs of the reconstructions were evaluated by three blinded observers (NK, GH, and PB) and scored for gross morphological appearance of the surface congruency of individual plugs (Table 1). Subsidence, protrusion, tilting, sclerosis, and fibrous overgrowth were considered to

Table 1 Macroscopic scoring system

Characteristics	Score
Clinical acceptable or flush—virtually no negative signs	2
Clinical suboptimal—minor negative signs	1
Clinical failure—obvious negative signs	0

Subsidence, protrusion, tilting, sclerosis, and fibrous overgrowth were considered as negative signs

be negative signs. The separate scores of each of both transplanted plugs were added, resulting in a maximum score of 4 per goat.

Microscopic preparation

The operated condyle was dissected with a diamond-coated and water-cooled sawing blade (blade thickness 300 μm) exactly in two halves in the AP direction through the center of the two plugs and photographs were taken again. Thereafter, two slices were made from each section plane of both halves of the defect and processed for histology.

The two slices were used for vitality testing with Cell Tracker Green CMFDA (5-chloromethylfluorescein diacetate; Molecular Probes, Invitrogen Ltd, UK) and propidium iodide (Molecular Probes, Invitrogen Ltd., UK). Directly following coloring, the specimens were photographed through a fluorescence photomicroscope (Zeiss Axioplan 2; Carl Zeiss BV, Sliedrecht, The Netherlands) and frozen afterward. In a later stage, they were defrosted and vital cells were colored by NADH-diaphorase (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) with nitroblue-tetrazolium (NBT; Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands). After taking photographs, these slices were further processed for routine histology as described below.

All specimens were fixated in a 4% buffered formalin solution (pH 7.4) for at least 1 day. The specimens were embedded in polymethylmethacrylate and sectioned (7-μm-thick sections) with a microtome (Leica RM 2155, Leica Microsystems Nederland BV, Rijswijk, The Netherlands), and stained with Hematoxylin and Eosin, Alcian Blue and Safranin O. Serial sections of the trochlear donor defect were prepared in the transverse direction.

Histological scoring

The reconstructions were graded for graft level with surrounding cartilage, graft cartilage thickness, cartilage integration, degenerative changes at cartilage edges, changes in tidemarks at cartilage edges, integration of adjacent subchondral bone, and subchondral cavity formation (Table 2). This scoring system was adapted from

Table 2 Histological scoring system

Characteristics	Score
Graft level with surrounding cartilage	
Level	4
<50% of graft cartilage thickness—below	3
<50% of graft cartilage thickness—raised	2
>50% of graft cartilage thickness—below	1
>50% of graft cartilage thickness—raised	0
Graft cartilage thickness	
75–100% of adjacent cartilage	2
50–75%	1
<50%	0
Cartilage integration	
Bonding through cartilage like tissue	3
Fissure fully filled with fibrous tissue	2
Fissure partially filled with fibrous tissue	1
Empty fissure	0
Degenerative changes at cartilage edges	
Normal cellularity, no clusters, normal staining	3
Mild hypocellularity, some clusters, moderate staining	2
Moderate hypocellularity, slight staining	1
Severe hypocellularity, poor or no staining	0
Changes in tidemarks at cartilage edges	
Both normal	2
One damaged or abnormal	1
Both damaged or abnormal	0
Integration of adjacent subchondral bone	
Fully osseous integration	4
Fully integrated with partial fibrous tissue	3
Fully integrated only fibrous tissue	2
Partially integrated	1
No integration	0
Subchondral cavity formation	
No cavities	3
Small cavities	1
Large cavity	0
Total maximum score per location	21

In each reconstruction, 3 locations were evaluated, the anterior host–plug contact area (A), the central plug–plug contact area (B), and the posterior plug–host contact area (C). The scores for each location were summed to obtain a total score for each reconstruction

similar scales for osteochondral cartilage repair published by other researchers [4, 22]. The same three blinded observers (NK, GH, and PB) scored two specimens from the center of the repaired defect independent of each other. In each reconstruction, 3 locations were evaluated, the anterior host–plug contact area (A), the central plug–plug contact area (B), and the posterior plug–host contact area (C). The scores for each location were summed to obtain a total score for each reconstruction.

Statistical analysis

Datasets from gross morphological scoring and histological grading were evaluated nonparametrically, as normal distribution could not be assumed for all parameters. Unpaired comparisons between bottomed and unbottomed plugs were made using the Mann–Whitney U test (Wilcoxon rank sum test). A P value <0.05 was regarded as statistically significant.

Results

Macroscopic scoring

The gross morphological scoring showed a significantly higher score for surface congruency in bottomed plugs as compared to unbottomed reconstructions ($P = 0.04$) (Table 3).

Microscopic scoring

No differences between local and total histological grading scores for bottomed and unbottomed plugs were found (Table 4).

Histology of the plugs

Both the NADH-diaphorase staining and the life dead assay showed a similar distribution of vital and necrotic cells (Fig. 2). Most chondrocytes of the host cartilage and transplanted plugs were vital (Fig. 2a, b, c). Necrotic

Table 3 Macroscopic scores

	Bottomed ($n = 9$)	Unbottomed ($n = 9$)	P value
Anterior plug	1.5 ± 0.4	0.8 ± 0.7	0.03
Posterior plug	1.2 ± 0.7	0.7 ± 0.8	n.s.
Total	2.7 ± 0.8	1.5 ± 0.4	0.04

Values are mean ± SD

n.s. = $P \geq 0.05$

Table 4 Microscopic scores

	Bottomed ($n = 9$)	Unbottomed ($n = 9$)	P value
A	11.1 ± 3.6	12.3 ± 3.0	n.s.
B	8.8 ± 3.0	9.7 ± 3.3	n.s.
C	12.3 ± 2.5	11.3 ± 3.7	n.s.
Total	32.0 ± 6.0	32.1 ± 8.5	n.s.

Values are mean ± SD. (A) anterior host–plug contact area, (B) the central plug–plug contact area, and (C) the posterior plug–host contact area

n.s. = $P \geq 0.05$

Fig. 2 Histology of sections stained with NADH-diaphorase with NBT (nitroblue-tetrazolium) for vitality (**a**, **b**, **c**) and section (**d**) in which living cells are stained with Cell Tracker *Green*. Notice difference in thickness between host (*H*) and plug (*P*) cartilage. In **b** the *lower square box* is a magnification of the *upper square box*. **a**, **b** bottomed reconstructions, **c**, **d** unbottomed reconstructions
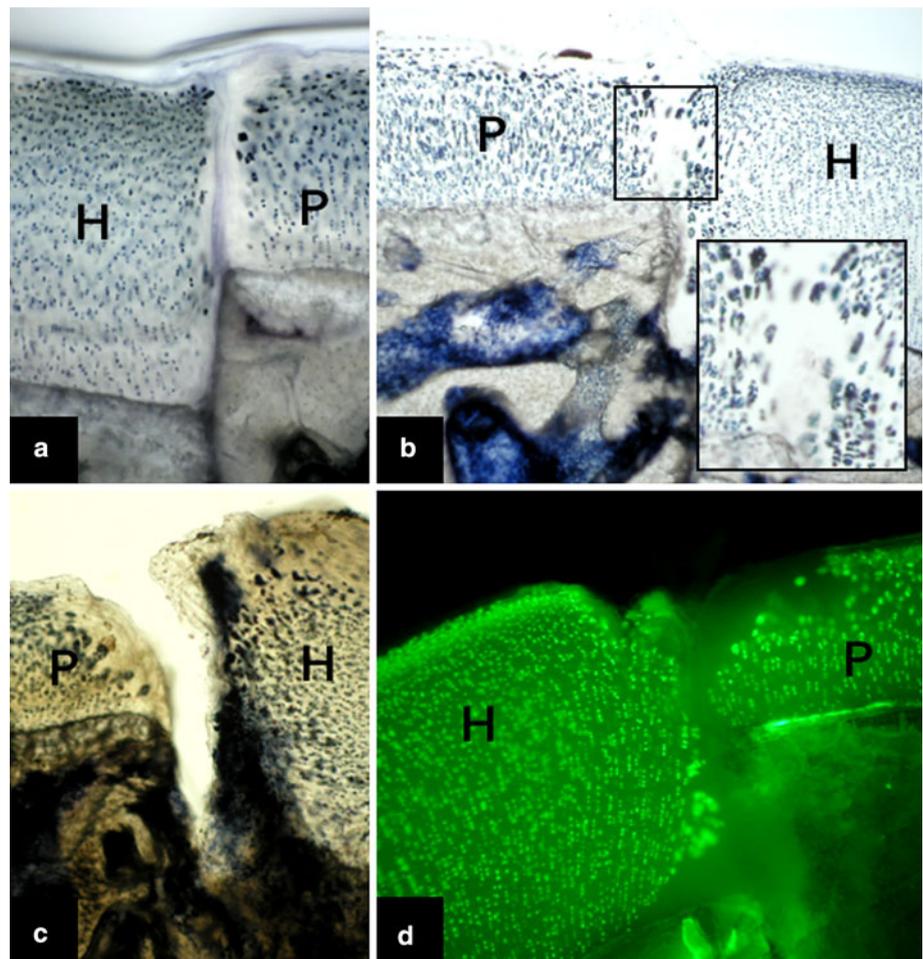
chondrocytes were present in equal low numbers in both host and plug articular cartilage. Only at the edges toward the interface between plugs, there was a thin acellular zone of cartilage (Fig. 2a, d). Bordering this acellular layer, clustered chondrocytes were present in almost all plugs and bordering host cartilage (Fig. 2b). Generally, plugs were in close contact with each other (Fig. 2a, b, d). Occasionally, larger gaps were also present (Figs. 2c, 3b). The cartilage interface between plugs was in most cases very thin and plugs seemed to be press-fit (Fig. 3a). No integration of cartilage in between plugs or between plugs and host cartilage was found.

Integrity of the tidemark

The tidemarks were generally intact (Fig. 4a). Particularly, if the subchondral bone was revascularized, small capillaries of the newly formed fibrous subchondral tissue were penetrating the tidemark, and by that, the integrity of the tidemark was reduced (Fig. 4b). Integration of neighboring tidemarks between neighboring plugs was never observed.

Subchondral bone remodeling

The central part of the subchondral bone of the transplanted plugs was still mainly avascular and necrotic with empty osteocyte lacunae and necrotic medullary tissue. From the deeper parts of the defect and from the interfaces with the host bone, a process of creeping substitution of the necrotic bone was present. This process was characterized by abundant osteoclastic resorption sites of the transplanted bone (Fig. 3c), new bone formation on the remnants of the bone of the plugs and bone remodeling. Most of the new bone was directly formed as woven bone (Fig. 3d); however, irrespective of the treatment group, in various locations in the subchondral areas, small areas of enchondral bone formation were present.

Donor site

Irrespective to the treatment modality, all donor sites showed rather similar histological appearances. In the defects, mainly fibrous tissue or fat marrow was present (Fig. 5a). Only at the edges of the defects in some cases,

Fig. 3 Routine histology staining of thin sections with Safranin O (**a**, **b**) and Haematoxylin and eosin (**c**, **d**). **a**, **c** bottomed plugs, **b**, **d** unbottomed plugs. **a** Notice cartilage-like tissue formation in the gap between the two inserted plugs (*P*). In **b** a larger nonfilled gap is present between host (*H*) and plug (*P*) cartilage. **c** Resorptive phase (*arrows* point at osteoclasts) in subchondral bone remodeling. **d** New bone formation in subchondral bone of transplanted plug
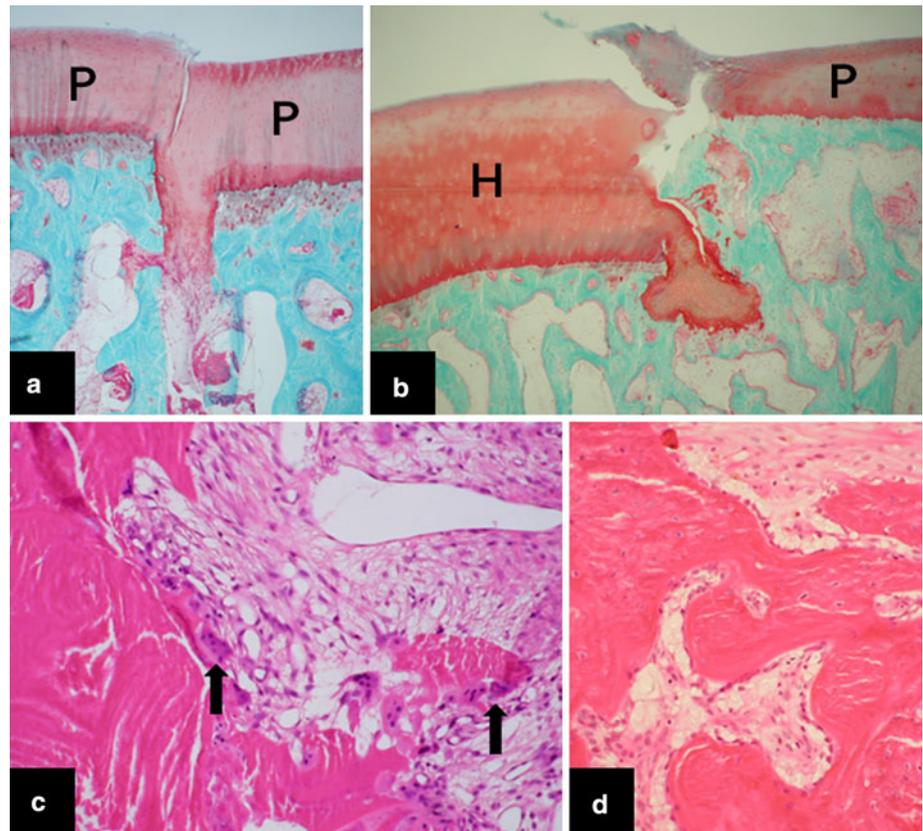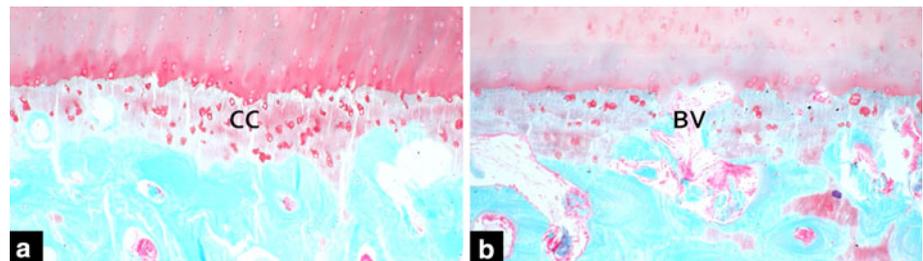

Fig. 4 Subchondral bone of host (**a**), and of unbottomed plug. *CC* is calcified cartilage. *BV* is a blood vessel penetrating to the tidemark

some focal areas of chondrogenic tissue were present. The surface of the newly formed tissue was either slightly depressed under the original contour of the defect or in a few cases it was elevated above the original contour (Fig. 5b), without clear correlation with the filling material in the defect. In only two defects that were filled with the hemostatic collagen type I sponge, centrally a few remnants of the original graft material could be found (Fig. 5c). In these cases, it was surrounded by some mononuclear lymphocytic cells but without a clear immunological reaction. In all defects that were filled with bone graft, this was completely resorbed without clear new bone formation. The edges of the donor site showed in all cases some form of depletion of the matrix, decreased chondrocyte vitality and clustering of chondrocytes (Fig. 5d).

Discussion

The most important finding of the present study was that chondrocyte vitality was maintained after osteochondral transplantation. On gross appearance, bottomed plugs seemed to reveal lesser subsidence tendency than unbottomed plugs; however, on histological evaluation, no significant differences could be detected between groups. In addition, the repair tendency of the donor defects was not improved by the two different filling techniques evaluated in this animal model.

Gross morphological scoring showed that the bottomed plugs performed superior in maintaining flush level with the surrounding subchondral bone. The fact that on histological scoring bottomed and unbottomed plugs failed to reveal a significant difference may be induced by the
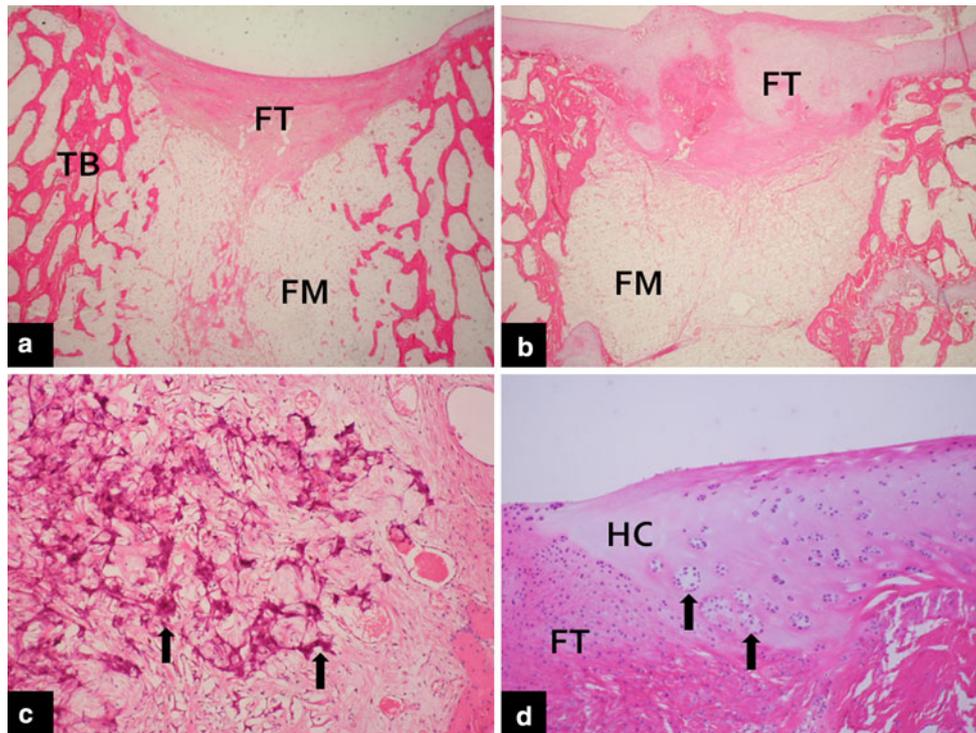
Fig. 5 a, **b** Haematoxylin and eosin-stained sections showing representative micrographs of donor site. **a** Empty defect. **b** and **c** defect filled with bone graft with spongostan. **c** Remnants of the collagen type I sponge (*arrows*). **d** Edge of host cartilage (*HC*) with clustered chondrocytes (*arrows*)

scoring method itself. The histological scoring was performed in the mid-sagittal plane only, whereas for macroscopic evaluation, the entire contour of the transplantation was judged and not just the appearance of the mid-sagittal plane (see also Fig. 6 for further explanation). Irrespective the fact that histological scoring was performed on the midsagittal plane only, it has to be recognized that no major differences were encountered between bottomed and unbottomed plugs. Clearly the extent of subsidence was relatively low in this animal model, which may be related to the compact subchondral bone structure of goats. Irrespective of the absence of a significant difference between the two groups, the evaluated different aspects of the histological score are still important parameters for the long-term success of the AOT technique. The most important long-term success aspect of the AOT technique above the ACI techniques or microfracture is the instantaneous restoration of the defect site with mature healthy hyaline cartilage, which was indeed confirmed in our study by an excellent chondrocyte vitality after transplantation.

Chondrocyte survival also appears to be dependent on the harvesting procedure of the osteochondral graft [11], where sharper cutting devices reduce the thickness of the layer of dead chondrocytes [12]. Moreover, harvesting by hand is superior above power trephine harvesting [5]. In

this study, only small margins of the plugs were acellular, indicating that indeed also limited chondrocyte death took place during the harvest. Besides the harvesting procedure, tampering the plugs into the bone might also induce chondrocyte death at the surface of the plugs. The fact that in both groups the surface layer was populated with vital cells indicated that the tempering probably did not induce a necrosis of the superficial chondrocytes. This indicates that the clinically used forces to insert plugs are most likely within the margin to induce cartilage damage, especially since goat cartilage is thinner and thereby more prone to damage, and higher tempering force is needed in the more compact goat bone, compared with human bone.

The potential for donor site morbidity is still a major drawback of the AOT technique and is held responsible for inferior results in some studies. For that reason, we evaluated some simple attempts to enhance the healing potential of these defects. However, filling the donor site defects with impacted cancellous bone, with or without a collagen type I layer, did not induce any new subchondral bone restoration as compared to empty defects. Although in the deeper parts of the defects some new bone was formed, there was no relation with the graft material.

This animal model on osteochondral transplantation has some clear limitations. Goats and sheep are widely
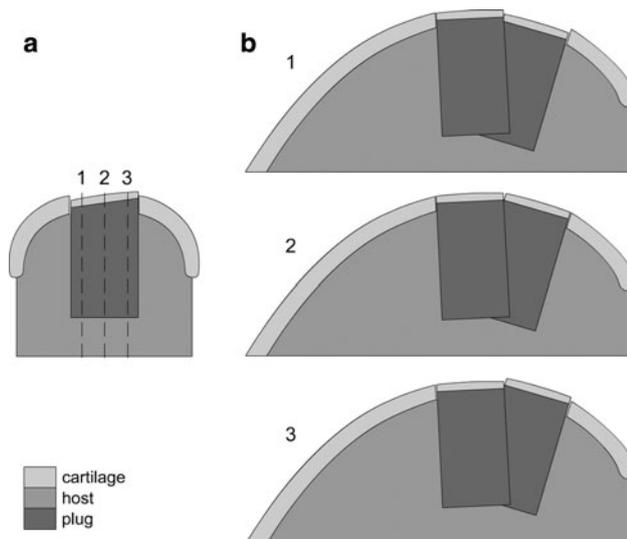
Fig. 6 Schematics for illustrating the possible discrepancy in judging the (flush) level of a whole graft through microscopic sections of the specimen. **a** Represents a sagittal view on the condyle. **b** Represents an A-P view of on the condyle. The *dotted lines* indicate the outer boundaries of the two thick sections, which were made. Notice the less than optimal perpendicularity of the plug's cartilage surface in respect to its subchondral bone in this schematic representation. **c** Represents the lateral view of the theoretical sections made at the *dotted lines* in **b**. *1* Notice the subsidence below flush level of the posterior (*right*) plug. *2* Notice the flush level of the posterior (*right*) plug. *3* Notice the protrusion above flush level of the posterior (*right*) plug

used large preclinical relevant models for human articular cartilage diseases. However, the results and recommendations from this study for patients should be carefully interpreted within the limitations of the model. Bone of healthy animals is of good quality and because of high loads more compact than in humans, which may have resulted in a more tightly press-fit placement of the plugs and thus a relative resistance to subsidence tendency. This phenomenon may have played a role in the encountered absence of a significant difference between 'bottomed' and 'unbottomed' groups on histological scoring.

Furthermore, it has to be recognized that in this study an osteochondral transplantation using the OATS® system was evaluated, which system on theoretical grounds may offer less intrinsic stability to the transplanted plugs than the alternatively available Mosaicplasty™ system. In contrast to the OATS® system, in the Mosaicplasty™ system, primary stability of the transplants is not only dependent on the standard shear forces between plug and host bone, but also on the conically shaped bottom part of the defect created by means of a dilator. The recommendation to bottom osteochondral plugs may thus mainly apply to the currently evaluated OATS® system.

Conclusions

Autologous osteochondral transplantation can indeed restore a joint defect with vital hyaline articular cartilage. Subsidence of the transplanted plugs may be detrimental for the eventual clinical outcome and should be avoided. In this animal model, using the OATS® system, macroscopic scoring revealed less subsidence tendency when the transplanted plugs were bottomed. In spite of the fact that the encountered benefit of bottoming was only limited in this animal model, bottoming is still recommended for clinical practice, especially when the OATS® system is used. Larger comparative clinical trials will be necessary to truly elucidate the potential clinical benefit of bottoming.

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