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**Knee Surgery, Sports Traumatology,
Arthroscopy**

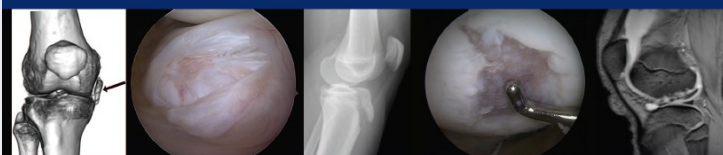
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Treatment of osteochondral defects: chondrointegration of metal implants improves after hydroxyapatite coating

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Abstract

Purpose The treatment of osteochondral defects in joint cartilage remains challenging due to its limited repair capacity. This study presents a metallic osteochondral plug with hydroxyapatite (HA)-coated cap edges for improved implant-tissue contact. The hypothesis was that improved attachment prevents from synovial fluid-influx and thereby avoids osteolysis and resulting implant instability.

Methods In total, 24 female, adult sheep were randomized into three groups. All animals received an Episealer[®]-implant in the medial condyle of the right knee. The implants were coated with two different HA versions or uncoated (control group). After 12 weeks, the implant-tissue connections were analysed radiologically and histologically.

Results In general, the groups with the coated cap edges showed a better quality of tissue connection to the implant. The occurrence of gaps between tissue and implant was more seldom, the binding of calcified and hyaline cartilage to the cap was significantly better than in the uncoated group. A histomorphometrically measured lower amount of void space in these groups compared to the group with the uncoated edges confirmed that.

Conclusions The hypothesis of a tighter cartilage bone contact was confirmed. The HA coating of the implant's cap edges resulted in better adherence of cartilage to the implant, which was not previously reported. In conclusion, this led to a better contact between implant and cartilage as well as neighbouring bone. In clinical routine, joint fluid is aggressive, penetrates through cartilage rifts, and promotes osteolysis and loosening of implants. The observed sealing effect will act to prevent joint fluid to get access to the implant-tissue interfaces. Joint fluid is aggressive, can cause osteolysis, and can, clinically cause pain. These effects are liable to decrease with these findings and will further the longevity of these osteochondral implants.

Keywords Osteochondral defect · Animal model · Knee · Resurfacing implant · HA coating · Histology

Introduction

The treatment of osteochondral defects remains a challenge and a number of treatment options, such as micro-fracturing [28], OATS [9], ACI [4], osteochondral grafts [8] and various combined techniques [19, 26] have been suggested.

In recent years, an additional treatment modality in the form of small metallic implants has received attention [3, 10, 32]. These implants are used as resurfacing agents after the lesion has been excised and are meant to reconstruct the plane of the original articulating surface. A first generation of implants [1, 2] uses a library of different articulating shapes whereas a second generation is manufactured from MR images by a CAD/CAM process [17, 25].

The treatment of cartilage lesions bears two challenges: first, the limited capacity of joint cartilage for intrinsic healing and second, the detrimental susceptibility of the subchondral bone to synovial fluid. The contact between joint fluid and subchondral bone is occurs only when cartilage tissue is destroyed.

Joint fluid represents a compartment of considerable metabolic flexibility and activity by numerous cytokines. The chemical composition changes in response to various

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influences such as trauma and inflammation and involves also degrading enzymes such as metalloproteases and collagenases [11]. Hence, synovial fluid not only lubricates the joint but also keeps away adhesences and cleans away debris. In direct contact with bony tissue, synovial fluid can also penetrate into cancellous bone and causes osteolysis and loosening of implants [5, 6, 13, 20, 21, 23, 30]. Hence, keeping synovial fluid out of implant–bone interfaces appears appealing.

The Episealer[®]-implant [25] for focal cartilage lesion resurfacing has a hydroxyapatite (HA) coating around the periphery of the implant. The joint cartilage faces these coated cap edges after insertion. Implants with uncoated cap edges served as controls. Within the here-reported sheep study, the adherence of cartilage to implants was tested in a controlled fashion. It is well known that HA is osteoconductive [27]. In contemporary orthopaedics, HA has become a universally accepted mode of fixation of implants to bone by osseointegration. This manuscript describes, for the first time, a similar effect of HA to cartilage, showing the phenomenon of chondrointegration. The HA-coated Episealer[®]-implant would offer a new clinical tool to treat small cartilage lesions to enable free joint movement without pain for several years. The cartilage defect would be sealed and the joint surface again smooth as the cartilage adheres to the implant surface. This may be one factor towards better longevity of cartilage resurfacing implants. The hypothesis is that HA shows chondro-inductive properties whereby the cartilage–implant interface, in essence, is sealed against the synovial compartment.

Materials and methods

Implant

The CT data of four sheep cadaver knees were averaged to create a semi-individualized implant of the Episealer[®] (Epi-surf Medical AB, Stockholm, Sweden) fitting for sheep in the desired weight range between 70 and 90 kg. The implant consisted of a cobalt–chromium alloy with a double coating of titanium and HA. The HA coating was restricted to the areas of the pin and the inner cap (group OHA). For the coated groups, HA was also applied on the outer cap edges. A previous study [16] has shown the standard HA coating (Osprovit[®], Eurocoating, Ciré-Pergine (TN), Italy) to be coarse and somewhat cracked. For this reason, a smoother (Bio-Coat, Orchid Orthopaedic Solutions, Detroit, MI, USA) HA coating was tested.

Animals

The Episealer[®] resurfacing implant was implanted in the medial condyle of the right knee (Fig. 1) in 24 adult female Merino-Mix sheep (79 ± 12 kg). The animals were randomized to the following groups: RHA group ($n = 8$), SHA group ($n = 8$), and OHA group ($n = 8$).

Surgery

In general, gas anaesthesia the right hind limb was prepared sterile. The animal was placed in the supine position, and received saline solution and eye ointment. As intraoperative pain medication, fentanyl was given every 30 min ($2 \mu\text{g/kg}$ BW Fentanyl-Janssen 0.5 mg, Janssen-Cilag GmbH, Neuss, Germany).

The knee was opened medially, the patella was dislocated laterally, and the medial condyle was exposed. A standardized guide was placed on top of the condyle, so that the hole-to-create would form in the middle of the load-bearing area. The guide was fixed with 3 Kirschner wires ($\varnothing 1.6$ mm) to the condyle. Then the cartilage incision was done using a cutting instrument after which a special drill was used to cut out a hole in the cartilage/bone to the appropriate depth. Positioning of the implant was made by a dummy; replica of the implant. Finally, the implant was inserted by gentle hammering until the implant was firmly fixed in the bone stock and the surface was smoothly adjusted to the surrounding cartilage. The joint was thoroughly flushed with sterile saline after which the wound was closed in layers.

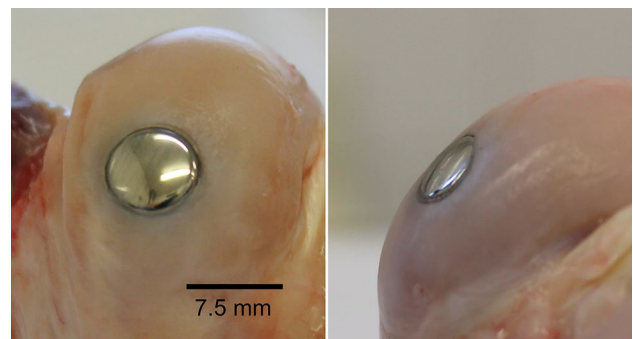


Fig. 1 The Episealer[®] implanted into the sheep's medial condyle in situ after 3 months healing time (after sacrifice). Note that the outer cap edges were either free of HA (group OHA) or coated with rough or smooth HA (groups RHA, SHA). The image shows the good quality of articular cartilage and the good surface restoration provided by the implant

Postoperative care

As pain medication, the animals received a transdermal fentanyl-plaster (Durogesic® SMAT 100 µg/h, Janssen-Cilag GmbH, Neuss, Germany). Additionally, 2.2 mg/kg of Flunixin-Meglumin were administered s.c. daily for the initial 7 days (Finadyne® RTS, Intervet Unterschleißheim, Germany). The animals showed a minor lameness after the surgery. The healing process went smoothly in all animals except one animal (group OHA). This animal showed continued severe non-relievable lameness on the operated leg, was euthanized prematurely, and excluded from the study.

Killing

After 3 months, the animals were killed with intravenously administered 2.5 g of thiopental sodium (Trapanal 2.5 g; Altana Pharma GmbH, Konstanz, Germany) and, after deep anaesthesia was confirmed, with 100 mL potassium chloride (1 M Kaliumchlorid-Lösung; Fresenius, Bernburg, Germany). The cardiac arrest was verified by auscultation.

After opening of the knee, a macroscopic examination was made by assessing the quality of the synovial fluid, the opposing tibial cartilage and the cartilage adjoining to the implant.

Histology

After dehydration in an ascending alcohol line, the samples including the implant were embedded in polymethylmethacrylate (PMMA: Technovit 7200 VLC, Heraeus Kulzer GmbH, Wehrheim, Germany). The embedded samples were ground down coplanar to a thickness of 80–100 µm (Mikroschleifgerät 400 CS, Exakt Apparatebau GmbH & CO.KG, Norderstedt, Germany).

The specimens were stained after Giemsa and analysed descriptively, by score, and by histomorphometry. In the descriptive histology, the quality of the joint cartilage adjacent to the cap edges was assessed. A good stainability, normocellularity and the absence of cartilage clusters were rated for a good cartilage quality, whereas a poor stainability with a hypo- or acellular cartilage tissue with chondrocyte clusters represents a bad cartilage quality.

With the histological score modified after the IRCS Visual-Histological-Score [14] and a score of O'Driscoll et al. [22], the grinding specimens were evaluated at the anterior and posterior edges of the implants. The overall impression of the specimen was scored as well as binding (gap), occurrence of different tissues, and the appearance of tissue quality (Table 1).

Histomorphometrically, the amount of tissue types at the implant border was measured. Every border of the implant should be in contact with tissue (exception: the joint surface)

and was accordingly marked manually. It was differentiated between hyaline cartilage, calcified cartilage, bone, soft tissue, and void space. The absolute values in mm were converted to percentage values according to the actual outline of the implant in the individual sample. The measurement accuracy of the image analysis system is at least one-tenth; therefore, results are reported with one decimal.

Ethical approval

All animal experiments were carried out according to the policies and principles established by the German national animal welfare guidelines, which are in accordance with the US Animal Welfare Act and the National Institutes of Health Guide for Care and Use of Laboratory Animals. The experiments were approved by the local ethics representative (LAGeSo Berlin, Germany, permit number: G 217/13).

Statistical analysis

In consideration of the 3R principles applied in animal studies, the sample size is kept to a minimum. Groups were calculated to $n = 8$ to reach a power of 0.8 and an effect size of 1.56. Normality of data was tested using the Kolmogorov–Smirnov test (KS test for normality). Results are given as mean \pm SD, data are compared using the Student's *t* test. A *p* value ≤ 0.05 is considered as statistically significant.

Results

Macroscopic assessment

At the time of harvesting, there were no indications of inflammation or wear debris in the joint. In all animals, the joint fluid was highly viscous, clear, and straw coloured. The opposing tibial cartilage had no macroscopically visible lesions in 19 out of 23 animals. Two animals showed a slight lesion of the superficial cartilage, while two other animals showed severe lesions down to the subchondral bone. Those two animals had a clearly protruding implant, in one sheep only laterally, and in the other sheep, it was protruding completely due to drill problems during surgery. All four affected animals showed no corresponding clinical symptoms during the observation time.

Descriptive histology

All implants showed a good bony integration of the pin- and inner cap regions. The subchondral bone is actively growing onto the implant, which can impressively be seen in the bone-filled thread at the end of the pin (Fig. 2). These areas were HA coated in all groups. The outer cap edges need to be

Table 1 Histology score with parameters and score points as applied to the samples in the study

Parameter	Description	Score points
Overall impression	Homogeneous	1
	Inhomogeneous	0
Integrity of implant	Normal	2
	With discontinuity, cysts	1
	Disintegration	0
Binding to hyaline cartilage	Binding at both sides	2
	Binding at one side/partial at both sides	1
	No binding	0
Binding to mineralized cartilage	Binding at both sides	2
	Binding at one side/partial at both sides	1
	No binding	0
Cell distribution	Cell columns	3
	Mixture cluster/columns	2
	Cell clusters	1
	Unorganized	0
Subchondral bone	Normal	3
	Increased remodelling	2
	Necrosis/granulation tissue	1
	Callus	0
Implant–bone contact	Trabeculi $\leq 350 \mu\text{m}$	1
	Non-existent	0
Absence of degenerative changes in adjacent hyaline cartilage tissue	Normocellularity, no clusters, normal stainability	3
	Normocellularity, no clusters, moderate stainability	2
	Slight–moderate hypocellularity, moderate stainab	1
	Severe hypocellularity, poor stainability	0
	Maximum score Σ	17

viewed more differentiated: in case of HA coating, in general a good direct bony contact with the implant was reached. This was secured by a direct contact between calcified cartilage and implant, which protected the delicate subchondral bone tissue against the synovial fluid and thereby prevented bone resorption processes (Fig. 3a, b). The uncoated group showed no or interrupted bony contact to the uncoated cap sides in 5 of 7 animals with mild to severe bone resorption processes (Fig. 3c, d).

Another main focus of the descriptive histology was the analysis of cellularity and stainability of the joint cartilage adjacent to the cap edges to judge the cartilage quality after 12 weeks of implant contact, and the tight connection between tissue (hyaline cartilage, calcified cartilage, bone, soft tissue) and implant (especially cap edges). Occurrence of gaps between tissue and implants were judged negatively since it compromises the overall stability of the implant on the long run.

Group RHA

Five of eight animals had chondrocyte clusters in the hyaline cartilage, with a good stainability in four of eight animals.

Two animals showed a moderate and two animals a poor stainability of the hyaline cartilage. Three of the eight animals showed hypo- to acellular cartilage areas. Overall, a good contact between implant and mineralized cartilage was found (Figs. 2, 3). In three out of eight animals, a gap between implant and tissue was visible, unilaterally in two animals and on both sides of the implant in one animal.

Group SHA

All animals showed chondrocyte clusters in the hyaline cartilage, with a good stainability in four of eight animals. Three animals showed a moderate, one animal a poor stainability of the hyaline cartilage. In five of eight animals, the hyaline cartilage was hypo- to acellular. In three out of eight animals, a gap was visible unilaterally between implant and tissue (Fig. 3).

Group OHA

The hyaline cartilage of this group was characterized by moderate (three out of seven) to poor (four out of seven) stainability and the occurrence of chondrocyte clusters in

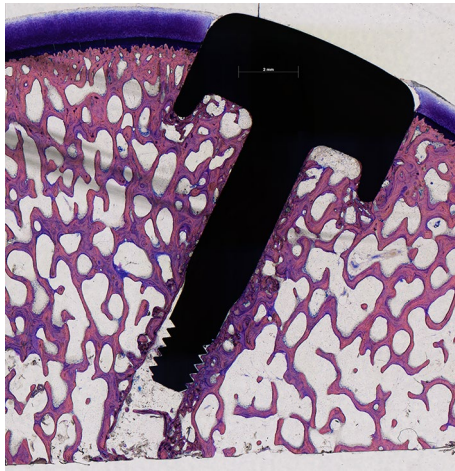


Fig. 2 Overview of a grinding specimen of an animal from group RHA, stained after Giemsa. The implant is visible in black, at the end of the pin tip, the thread is visible. The anterior part of the condyle is on the right; the posterior side is on the left. Due to lower loading conditions in the anterior condyle, the joint cartilage is thinner and less good stainable anteriorly. The subchondral bone is stained in rose. The thin line of calcified cartilage is stained in deep-dark purple and shows a good attachment to the cap edges of the implant. The overlying hyaline cartilage is stained purple and shows a 50% attachment (regarding the depth of the cartilage layer) on the posterior implant–tissue border, whereas there is no noteworthy attachment anteriorly

all seven specimens. All specimens showed hypo- to acellular cartilage tissue. In five specimens of this group, a gap between implant and mineralized cartilage was visible, that started at the surface and was running down in the depth of the tissue to different degrees, but always reaching to the subchondral bone. The width of the gaps was individually different. The gap was bilaterally visible in three animals, two animals showed a gap on the anterior side of the implant (Fig. 3). Consequentially, hyaline cartilage and implant were not in contact. The differences in tissue quality were small between the groups, while there were clearly more gaps between implant and bone/cartilage in the uncoated implants group.

Semi-quantitative histology score

The results for the histological scoring (Table 2) of the tissue adjacent to the implant showed a significantly better binding to calcified and adjacent cartilage of the SHA group ($p=0.043$, each) and of the RHA group [n.s. (non-significant), each] compared to the OHA group. Moreover, the absence of degenerative changes is by trend higher in the SHA group than in the OHA group (n.s.). The SHA group additionally shows a more homogeneous overall impression than the RHA group ($p=0.033$).

Histomorphometry

When histomorphometrically comparing the tissues at the cap edges, groups RHA and SHA show more hyaline cartilage and less void space than group OHA (Table 3). Both coated groups showed significantly lower values for the void space (RHA vs. OHA: $p=0.014$, SHA vs. OHA: $p=0.047$), which means, there was more tissue–implant contact in the coated groups compared to the uncoated group (OHA). The measured values for hyaline cartilage at the cap edges seemed to be higher in groups RHA and SHA compared to OHA, but this was not significant due to the high standard deviation. The values for mineralized bone, calcified cartilage, and connective tissue were equal in all groups. There were no differences between the two HA coatings.

Discussion

The most important finding of the present study was that chondrointegration is possible to a certain extent.

A good healing result for an osteochondral implant like the Episealer® would be a good integration of the implant in the bone, as well as in the cartilage stock. The successful integration in the bone stock would result in a stable implant situation, allowing biomechanical loading of the implant during physiological loading of the joint, and would be characterized histologically by homogenous bone trabeculi growing onto the implant surface without gap formation between implant and bone. Ideally, also no gap formation would occur between implant and cartilage. This basic requirement is more difficult to reach due to the tissue-specific characteristics of cartilage tissue, but fundamental to protect the underlying bone stock against the contact with synovial fluid and the thereby induced erosions or osteolysis.

This study analysed the healing process of osteochondral defects in sheep closed by an Episealer®. This mini-prosthesis, consisting of a cobalt–chromium alloy with a double coating of titanium and HA, resurfaces the joint surface. It is designed to cover osteochondral defects to eliminate pain, to restore joint functionality, and finally to postpone or avoid replacement surgeries. For this study, three variants of the outer cap edges were created: with rough (R)HA, with smooth (S)HA, and uncoated/without (O)HA.

The joint cartilage faces these outer cap edges after insertion. It is well known that HA is osteo-conductive [27] and this is currently used in routine orthopaedic surgery [24, 31]. The hypothesis was that HA, besides the known osteo-conductive properties, would additionally be “chondrophilic” by showing chondro-inductive qualities. In consequence, the cartilage–implant interface would be sealed.

These hypotheses were in general confirmed by the histological and histomorphometrical analyses performed in this

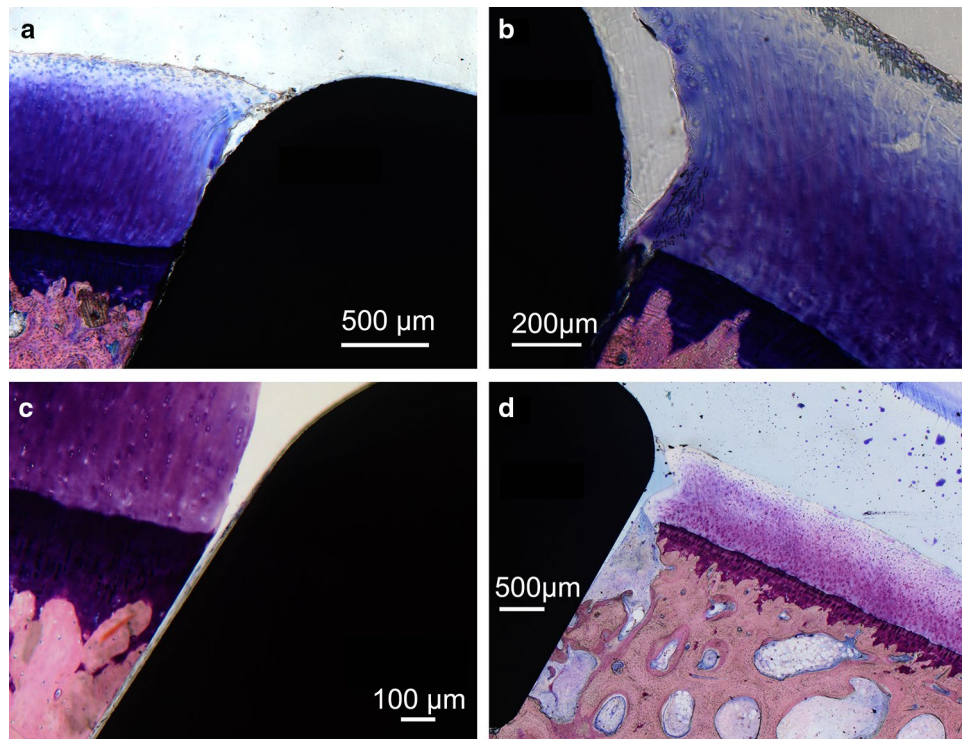


Fig. 3 Quality of contact between implant (black) and cartilage tissue (purple) as characteristic in this study for HA-coated and uncoated cap edges. **a** Good contact of both, calcified and hyaline cartilage with the implant (cap edge coated). **b** Good contact of calcified cartilage and implant, although the implant is implanted approximately 0.1 mm too deep. Thereby the contact between cartilage and coated cap edges is hindered (cap edges coated). **c** Occurrence of a thin, but

penetrative gap between cartilage (and also bone) tissue and implant (cap edges uncoated). **d** Occurrence of a broad gap, reaching deep into the subchondral bone, with resorptive processes in the adjacent tissue, probably due to contact with the synovial fluid. The bone itself, at least in the deeper regions, seems to be vital with pinkish osteoid-seams (cap edges uncoated)

Table 2 Results of the histology score for the three different groups displayed as mean values \pm SD

Parameter	RHA	SHA	OHA	Max. score
Overall impression	$0.5 \pm 0.5^{**}$	$1.0 \pm 0.0^{**}$	0.9 ± 0.4	1
Integrity of implant	1.4 ± 0.5	1.6 ± 0.5	1.3 ± 0.5	2
Binding to adj. cartilage	1.4 ± 0.4^i	$1.5 \pm 0.5^*$	$0.7 \pm 0.8^{*i}$	2
Binding to calc. cartilage	1.4 ± 0.5^i	$1.5 \pm 0.5^*$	$0.7 \pm 0.8^{*i}$	2
Cell distribution	1.8 ± 0.7	2.0 ± 0.5	1.6 ± 0.8	3
Subchondral bone	2.4 ± 0.7	2.0 ± 0.8	2.3 ± 0.8	3
Implant–bone contact	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1
Absence of deg. changes	1.1 ± 1.0	$1.8 \pm 0.7^{\#}$	$1.1 \pm 0.4^{\#}$	3
Maximum score	10.5 ± 4.2	12.1 ± 2.3	9.9 ± 2.4	17

There were some differences found between the three groups with the help of this semi-quantitative score: the SHA group shows (1) a significant better binding to calcified and adjacent cartilage than the OHA group ($*p=0.043$, each), and (2) a significantly more homogeneous overall impression than the RHA group ($**p=0.033$). The SHA group also shows a tendency for a higher absence of degenerative changes compared to the OHA group ($^{\#}p=0.059$). The RHA group shows by trend a better Binding to calcified and adjacent cartilage compared to the OHA group ($^i0.079$, each)

study. The HA coating of the implants cap edges resulted, besides good bone ongrowth, in better adherence of calcified and also hyaline cartilage to the implant. Hence, HA coating is able to promote calcified cartilage adherence to

metal implants. This process could be observed on every HA-coated Episealer[®] and could be characterized as chondrointegration. To our knowledge, this has not been reported previously.

Table 3 Histomorphometrical parameters measured in the different groups and expressed as percentage of the absolute values

Group	Hyaline cartilage		Calcified cartilage		Mineralized bone		Connective tissue		Void space	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RHA	4.2	± 3.5	1.4	± 1.1	64.4	± 11.5	27.5	± 13.6	2.4	± 2.7**
SHA	3.9	± 1.7	1.5	± 1.0	62.8	± 11.1	27.8	± 8.6	3.9	± 5.1 [#]
OHA	2.5	± 2.5	1.1	± 1.1	61.8	± 11.0	22.1	± 11.1	12.3	± 9.5***

Both coated groups show a significantly (** $p=0.014$, [#] $p=0.047$) lower amount of void space around the implant compared to the uncoated group OHA

The HA coatings in this study were shown to improve the contact of calcified and hyaline cartilage to the implant. This sealing effect would prevent the bone from contact with synovial fluid. Joint fluid is capable of penetrating a variety of tissues [12, 29] around the knee and the unfavorable effects of joint fluid in the context of TKA is well known [7, 18]. Cystic lesions caused by joint fluid seem to be initiated by two parallel mechanisms that might amplify each other. On the one hand, the pressurized fluid alters the bone loading conditions in terms of decreasing the load on the surrounding bone. This leads to bone resorption and growth of the cystic lesion. On the other hand, the pressurized fluid causes osteocytes death, which again and additionally leads to bone resorption. In fact, the animals of this study showed no cystic lesions in the subchondral bone, but gaps occurred between implant and tissue, significantly more in the uncoated group. These gaps between implant and cartilage can be the starting point for cystic lesions and, therefore, initiate implant loosening. Bone cysts can develop in the course of months and tend to be painful for the patient [6, 30]. Hence, preventing joint fluid to access the tissue–implant interface may be a decisive factor to promote good long-term performance.

The Episealer[®] implant has been tested pre-clinically [15–17], and is now in clinical use in ≈ 400 cases over a 65-month period with satisfying clinical results. Less than 10 revisions have, so far, been reported at the time of this writing (last author, personal communication).

This animal study has limitations which should be mentioned: in contrast to the pre-clinical tests in human patients, the sheep's implants were manufactured in a semi-individual manner. That implicates that implants were not fitting completely to the individual sheep's anatomical situation: the curvature of joint and implant surface could differ and lead to protruding implants. Moreover, the radius of the implants edge was kept at 1 mm and the HA coatings stopped at the beginning of the radius. Since sheep cartilage is about half as thick as human cartilage, these facts led to the HA coating sometimes facing only the deep/calcified portion of the cartilage. These facts introduced considerable noise in the study. Nevertheless, the superiority of HA coating over non-coated implants

was statistically significant and our hypothesis has been confirmed. Finally, the miniaturization of the implant and instruments proved difficult to handle technically, resulting in less than optimal positioning of some of the implants.

In a future study, the long-time outcomes of coated vs. uncoated implants should be evaluated. By focussing on the occurrence of cystic lesions in the subchondral bone initiated by gaps between implant and tissue, the protective effect of the sealing HA coating could be verified.

In contemporary orthopaedics, HA has become a universally accepted mode of fixation of implants to bone by osseointegration. The described phenomenon of chondrointegration initiated by the HA coating could effect a better longevity of cartilage resurfacing implants improving the life quality of the patients and simplifying clinical routine.

Conclusion

In conclusion, the coating with HA led to a better contact between implant and tissue and less void space. This could have clinical consequences in terms of better longevity of HA-coated implants, possibly postponing the need for a second, and more extensive intervention to retain the joint function.

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Compliance with ethical standards

Conflict of interest Hanna Schell, Elisabeth Zimpfer, Katharina Schmidt-Bleek, Tobias Jung, and Georg N. Duda declare that they have no conflict of interest. Leif Ryd is board member and medical advisor of the Episurf Medical.

Ethical approval All procedures performed in this study involving animals were in accordance with the ethical standards of the institution or practice at which the study was conducted.

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