Osteoarthritis and Cartilage 22 (2014) 836–844

Osteoarthritis and Cartilage

Fixation of a double-coated titanium-hydroxyapatite focal knee resurfacing implant
A 12-month study in sheep

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ARTICLE INFO

Article history:
Received 25 October 2013
Accepted 30 March 2014

Keywords:
Focal cartilage lesion
Focal knee resurfacing
Metal implants
Osseointegration
Sheep animal model

SUMMARY

Objective: Focal cartilage lesions according to International Cartilage Repair Society (ICRS) grade 3–4 in the medial femoral condyle may progress to osteoarthritis. When treating such focal lesions with metallic implants a sound fixation to the underlying bone is mandatory. We developed a monobloc unipolar cobalt-chrome (Co-Cr) implant with a double coating; first a layer of commercially pure titanium (c.p.Ti) on top of which a layer of hydroxyapatite (HA) was applied. We hypothesised that such a double coating would provide long-lasting and adequate osseointegration.

Design (materials and methods): Unilateral medial femoral condyles of 10 sheep were operated. The implants were inserted in the weight-bearing surface and immediate weight-bearing was allowed. Euthanasia was performed at 6 (three animals) or 12 months (six animals). Osseointegration was analysed with micro-computer tomography (CT), light microscopy and histomorphometric analyses using backscatter scanning electron microscopy (B-SEM) technique.

Results: At 6 months one specimen out of three showed small osteolytic areas at the hat and at 12 months two specimens out of six showed small osteolytic areas at the hat, no osteolytical areas were seen around the peg at any time point. At both time points, a high total bone-to-implant contact was measured with a mean (95% confidence interval – CI) of 90.6 (79–102) at 6 months and 92.3 (89–95) at 12 months, respectively.

Conclusions: A double coating (Ti + HA) of a focal knee resurfacing Co-Cr implant was presented in a sheep animal model. A firm and consistent bond to bone under weight-bearing conditions was shown up to 1 year.

Introduction

Full thickness cartilage injuries beyond a certain rather small size (4–7 mm in sheep) do not heal instead they may develop to osteoarthritis[1–4]. Hence, treatment is warranted but is still controversial and remains an unsolved clinical challenge[5]. The treatment of cartilage injuries evolves along two dichotomously differing approaches. On one side there are attempts at biological healing by means of cell stimulation of different kinds (autogenous chondrocyte implantation – ACI, mosaicplasty or simple microfracturing). As of yet there is insufficient evidence to state which of these methods is superior[6–9]. The alternative approach is to resurface the cartilage defect with a metallic implant[10–13]. If the latter is chosen, sound fixation to the underlying bone is mandatory. Focal cartilage injuries are being treated more frequently with metallic resurfacing implants in human joints although data on osseointegration are still scarce and only a few animal studies present promising but varying results[11,14,15]. In this report we describe the osseointegration process up to 1 year postoperatively in a sheep animal model.

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http://dx.doi.org/10.1016/j.joca.2014.03.019
1063-4584/

When fixating a small unipolar (articulating against opposing cartilage) focal knee resurfacing (FKR) implant distinct challenges are encountered. First, in this middle-aged patient group bone should be spared, should future intervention be needed. Existing FKR implants use large penetrating anchoring screws fixating to metaphyseal condylar bone, potentially creating large defects upon removal and hence augmenting complexity of revision surgery[16]. For the same reason polymethylmethacrylate (PMMA) cement is generally avoided in the younger patient (<50 years)[17]. Secondly, a firm fixation warrants a tight sealing between the implant and surrounding tissue, as penetration of joint fluid into the implant–bone interface is prone to induce osteolysis and subsequently implant loosening[11]. Additionally, previous studies have shown that FKR implants should not protrude but rather be recessed in relation to surrounding cartilage level, in order not to damage the opposing tibial cartilage[11,13,18]. Thus, a secure yet highly accurate fixation method and instrumentation is demanded.

We developed a slender monobloc implant with a double coating on a cobalt-chrome (Co-Cr) core for non-cemented fixation. First a coating of commercially pure titanium (c.p.Ti) was used, on top of which a superficial layer of hydroxyapatite (HA) was applied. In this first report we introduce the double coating for FKR fixation, and hypothesised that this method should provide a long-lasting secure fixation of the implant to the bone. Such a durable bond would be created first by ongrowth of bone to the HA layer and secondly, should the HA dissolve, by the establishment of a permanent bone-titanium bond.

Materials and methods

Animals

Ten healthy female sheep (Swedish landrace) from the same breeder were operated and housed at the Department of Clinical Sciences, Swedish University of Agriculture Sciences (SLU) in Uppsala, Sweden. One animal was euthanized 2 months postoperatively and data are reported from the remaining nine animals. The mean age and weight of sheep was 4 years (range 2–6) and 74.4 kg (range 62–90), respectively. The animals were kept indoors in stables in groups of three. Food was given twice a day and water was freely available. Well-known personnel monitored the animals daily for general condition, signs of pain and lameness (where grade 0 was normal gait and 1–4 was mild, moderate, major and severe lameness respectively). Euthanasia was performed after 6 months in three animals, and six animals were euthanized after 12 months. Animal Ethics Committee, Uppsala, Sweden, approved the protocol.

Implant

The implants (diameter 7.5 mm) had a double-curved (radii 19 and 12 mm) articulating surface, modelled after computer tomography (CT) scans of a standard sheep knee and manufactured from implant-grade Co-Cr by computer aided design and manufacturing (CAD/CAM) process. The implants were coated with commercially pure titanium (60 μm) on which a layer of HA (60 μm) was plasma-sprayed (Plasma Biotal Ltd., Buxton, GBR). A 10 mm peg (diameter 2 mm) was introduced into an undersized (diameter 1.8 mm) drill hole in the bone for primary interference fit. The implants were manufactured and provided by Episurf AB, Stockholm, Sweden.

Anaesthesia

The animals were anaesthetized by an intravenous (IV) injection in the jugular vein of xylazine (Rompun® vet, Bayer Animal Health, Lyngby, Denmark) 0.11 mg/kg and ketamine (Ketaminol® vet, Intervet, Stockholm, Sweden) 2.2 mg/kg after which they were intubated. The anaesthesia was maintained with isoflurane (IsoFlo® vet, Orion Pharma Animal Health, Stockholm, Sweden) 1.5–3% in 100% oxygen. All animals breathed spontaneously. After anesthetization, blood samples were taken from the cephalic vein. The animals were given antibiotics, cefuroxime (Cefuroxim, Farmaplus, Oslo, Norway) 22 mg/kg IV and analgesic, carprofen (Rimadyl® vet, Orion Pharma Animal Health, Stockholm, Sweden) 4 mg/kg subcutaneously (SC), buprenorphine (Temgesic®, Schering-Plough, Stockholm, Sweden) 0.01 mg/kg intramuscularly (IM), glykopyrrolate (Robinul®, Meda, Solna, Sweden) 0.25 ml/10 kg SC. The animals were operated in dorsal recumbency and the surgical field was aseptically prepared.

Surgery

Surgery was performed on one knee; randomly prepared closed envelope determined the side. All operations were carried out under aseptic conditions by the same surgeons (HNS, NMC and LR). The medial femoral condyle was exposed through a medial parapatellar 5–6 cm incision through skin and subcutaneous tissue. After inspecting the knee the operation was carried out using a set of specially designed instruments: First, a centralising aiming guide with a built-in guiding tube, adapted to the contour of the posterior weight-bearing condylar surface was applied and fixed to the condyle by means of three pins engaging the metaphysis outside the articulating cartilage. Through the guiding tube, positioned perpendicular to the articulating surface, a specially designed drill was used to cut the cartilage and the underlying bone in a way to exactly correspond to the shape of the implant. According to previous studies[13], we aimed to position the implant at a level 0.5 mm recessed below the surrounding cartilage. A slightly smaller testing device with identical articulating contour as the final implant was subsequently used to control the position in height relative to the surrounding cartilage before finally inserting the implant. Finally, the joint capsule was sutured in a continuous pattern using polydioxanone (PDS®, Ethicon) and the subcutaneous tissue and skin were closed in a similar pattern using polyglicaprone 25 (Monocryl®, Ethicon). No surgical complications occurred during the operations. The sheep were extubated in their stables and under continuous observation and regained consciousness within 1-h postsurgery. The animals were randomly sacrificed at 6 months (three animals) or after 12 months (six animals) using an overdose pentobarbital (100 mg/ml) after securing blood samples. The knees were removed from the body and the joint was inspected macroscopically, according to ICRS (0–4) and a modified O'Driscoll score (0–6 points instead of 0–10) as the parameter restoration of contour and cartilage erosion of the graft was not possible to evaluate[14,19,20]. Also, imaging and histological assessments were performed.

Micro-CT

The specimens were scanned using a high-resolution micro-CT system (μCT 40, Scanco Medical, Switzerland) in multislice mode. Each image data set consisted of approximately 600 horizontal micro-CT slice images perpendicular to the long axis of the peg. The specimens were scanned in high-resolution mode with an *x*-, *y*-, *z*-resolution of 16 μm. The image data sets were used to produce 3D views of the specimens using a software program (Scanco Medical, Switzerland).

Light microscopy

The specimens were prepared for light microscopy according to the ground sectioning technique by Donath and Breuner[21]. In short, the specimens were dehydrated in a graded series of ethanol: 60%,

80%, 96% and absolute ethanol for 48 h each. Then the specimens were infiltrated with a graded series of ethanol and Technovit 7200 VLC (Kulzers, Germany) embedding resin over a period of at least 12 days at standard temperature and pressure while constantly shaking. Finally the samples were placed in three consecutive containers of 100% Technovit 7200 VLC (Kulzers, Germany) for 24 h each at standard temperature and pressure and constant shaking. Following dehydration and infiltration the specimens were light polymerized in Technovit 7200 VLC for 10 h using a light polymerization unit (Exakt, Norderstedt, Germany) equipped with water cooling. The temperature during polymerization never exceeded 40°C. In the following the polymerized blocks were sectioned using a band-saw unit (Exakt, Norderstedt, Germany) equipped with a diamond coated band. The sections were ground to a thickness of 30–50 μm using an Exakt microgrinding unit. The sections were polished stepwise using Struers diamond pastes. The sections were stained with Sanderson's Rapid Bone Stain and counter stained with acid fuchsin (both Dorn & Hart, USA). Sections were cover slipped for light microscopic evaluation.

Histomorphometric analyses

The amount of the bone-to-implant contact was measured with ImageAccess software (Imagic, Glattbrugg, Switzerland). The measurement was started from the first bone-to-implant contact at the left side of the hat around the body of the implant to the first bone contact at the right side. Bone density was measured in a 500 micron wide area around the implants and in a corresponding section of normal host bone from the same region distant to the implant using the phase analysis module of ImageAccess (Imagic, Glattbrugg, Switzerland).

Backscatter scanning electron microscopy (B-SEM)

For the B-SEM evaluation, the specimens were glued on an aluminium holder. The surface to be examined was highly polished with diamond pastes and thoroughly cleaned in an ultrasonic cleaner. Thereafter the polished surface was coated with a 6 nm thick carbon layer using an SCD-500 sputter coater (Leica, Microsystems, Heerbrugg, Switzerland). The specimens were examined with a Zeiss Supra VPN-40 field cathode scanning electron microscope using the backscatter detector. The resulting images were evaluated using ImageAccess (Imagic, Switzerland) software. The amount of the bone-to-implant contact was measured in percentage.

Statistics

This report is largely descriptive and data are presented as means with their range or estimated 95% confidence intervals. Means for each animal was used as independent samples. The Mann–Whitney *U* test for ranked values (SPSS 15.0 for Windows) was used to compare results at different time points; where a test statistic (*Z*-score) exceeding 1.96 is required to indicate statistical significance. *P*-value was set at 0.05.

Results

General and joint health of the animals

The general health of the sheep was good. One sheep was sacrificed due to pneumonia after 8 weeks. The wounds healed without complications. During the first week all sheep had various grades of limp (2–3) The lameness decreased gradually and after 4 weeks, three of the sheep showed minor limp (1–2 degrees). Postoperatively at 5, 9 and 12 weeks, respectively, no sheep had a limp. Joint health as indicated by the modified O'Driscoll score showed no changes in range of motion (ROM), fibrosis or cartilage appearance (average 0.0 out of maximum 6 points at 6 or 12 months). Likewise ICRS macroscopic score of the tibial surface showed no damage (average 0.0 points out of maximum 4 points) at 6 months and 0.67 (95% CI: −0.16, 0.51) points following 12 months indicating no statistical significance ($Z = 0.77$; <1.96).

Micro-CT evaluations

Approximately 600 horizontal scans per specimens were obtained. Figure 1 shows the scans at three horizontal levels through the peg: level 1 was positioned directly under the hat and level 3 at the end of the peg. The additional scan was positioned inbetween. At 6 months one specimen out of three showed small osteolytic areas beyond the hat, whereas the peg always was firmly osseointegrated. The other two specimens were completely osseointegrated. At 12 months, two specimens out of six showed small osteolytic areas at the hat. One specimen showed enlarged bone marrow chambers. The remaining three specimens were completely osseointegrated.

Light microscopic evaluations

Stained ground sections cut longitudinally through the centre of the peg showed functionally osseointegrated implants after both, 6 (Fig. 2) and 12 months (Fig. 3), respectively. Table I gives the percentages of bone-implant contact (BIC), marrow-implant contact (MIC) and connective tissue-implant contact (CTIC). At both time points, a high bone-to-implant contact was measured with a mean of 90.6 (95% CI: 79.4, 101.9) % at 6 months and 92.3 (95% CI: 89.5, 95.2) % at 12 months, respectively (Table I), indicating no statistical significance ($Z = 0.00$; <1.96). The mean bone density in a 500

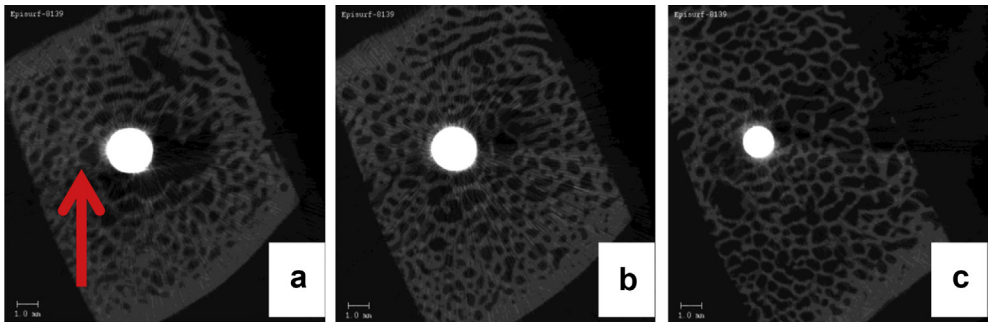

Fig. 1. Micro-CT scans of a 12-month specimen obtained directly below the hat (a), along the stem (b) and at the end of the stem (c). Note the osteolytic area below the hat (red arrow).

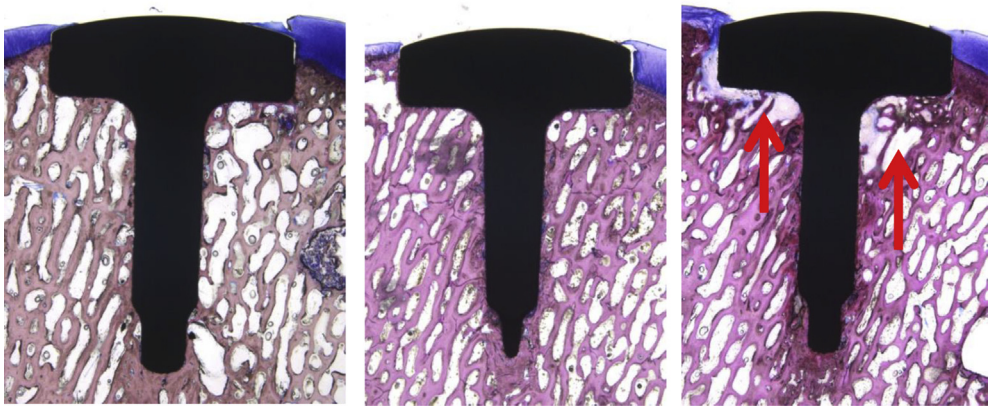

Fig. 2. Ground sections of the three 6-month specimens. Note the perfect osseointegration of the stem in all specimens. Also note the osteolytic areas (red arrows) below the hat in one specimen (red arrows).

micron wide band adjacent to the implant surface was 72.5 (95% CI: 60.0, 85.0) % at 6 months and 75.4 (95% CI: 67.3, 83.5) % following 12 months, respectively (Table II), indicating no statistically significant difference ($Z = 0.60$; <1.96). In the corresponding section of normal host bone distant to the implant the mean bone density was 63.0 (95% CI: 58.1, 68.0) % at 6 months and 48.7 (95% CI: 43.3, 54.2) % following 12 months, respectively (Table III). Overview of ground sections confirmed the presence of osteolytic areas beyond the hat in one 6-month specimen (Fig. 2) and in two 12-month specimens (Fig. 3) as revealed by the micro-CT technique.

Higher magnifications of the bone to HA interface revealed an excellent osseointegration by intimate contact between bone and the HA coating (Fig. 4). In areas of bone marrow in contact with the HA coating, the latter became partially or completely dissolved (Fig. 5). Single or clumps of HA particles were observed in the bone marrow chambers near the implant surface [Fig. 5(b)]. Macrophages were observed either in contact with the HA layer undergoing disintegration or engulfing the HA particles in the bone marrow [Fig. 5(b)]. Inflammatory reactions were not observed in marrow chambers adjacent to areas of HA destruction. The exposed plasma-sprayed titanium coating did not show signs of disintegration. In contrast, new bone formation by osteoconduction occurred along the implant surface leading to newly formed bone deposited directly on the exposed titanium sprayed surface [Fig. 5(d)].

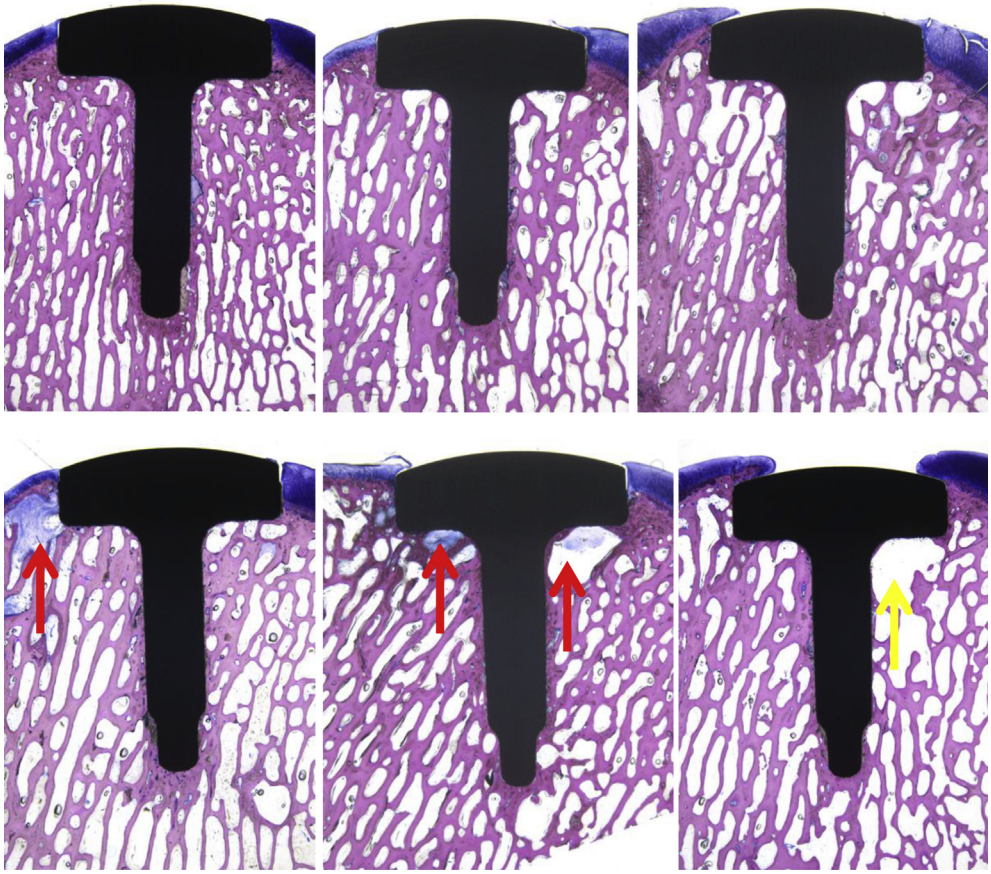

Fig. 3. Ground sections of the 12-month specimens. Note the perfectly osseointegrated stem of all specimens. Also note the presence of osteolytic areas (red arrows) in two specimens, and a widened marrow chambers in one specimen (yellow arrow).

Table I
Percentage of both, bone-implant contact (BIC), marrow-implant contact (MIC) and connective tissue-implant contact at 6 months and 1 month, respectively

Time	Sample ID	BIC (%)	MIC (%)	CTIC (%)
6 m	6446	80.2	7.7	12.1
	7169	100	0	0
	8261	91.7	8.3	0
	Mean	***90.6***	***5.3***	***4***
	SD	*9.9*	*4.6*	*7*
12 m	5025	90.9	3	6.1
	5040	92.3	7.7	0
	5051	91.8	4.9	3.3
	5067	97.9	2.1	0
	7111	89.6	4.2	6.2
	8139	91.5	8.5	0
	Mean	***92.3***	***5.1***	***2.6***
	SD	*2.9*	*2.6*	*3*

Table III
Bone density in a corresponding wide band of normal sheep bone from the same region distant to the implant

	Bone %	Marrow %
6 months		
6446	58.1	41.9
7169	64.5	35.5
8261	66.5	33.5
Mean	***63.0***	***37.9***
1 year		
5025	47.8	52.2
5040	42.9	57.1
5051	42.7	57.3
5067	56.1	43.9
8139	54.2	45.8
Mean	***48.7***	***51.3***

Osteolytic areas next to the sides of the hat and below the hat were filled with connective tissue (Fig. 6). No signs of an inflammatory reaction could be observed in the connective tissue. Ongoing resorption of bone by osteoclast activities was absent at both time points. In contrast, repair of bone was repeatedly observed at both time points, outgoing from bone trabeculae framing the defect (Fig. 6).

There was often an artificial cleft between the cartilage and the cobalt-chromium hat, either due to a slight shrinkage of the cartilage during specimen preparation for histology or due to mechanical stress during the cutting and grinding processes [Fig. 7(a)]. However in the sections where cartilage interfaced against HA, there was a distinctly better adherence with a mean 86% contact. The cartilage *per se* looked viable and unchanged with no signs of apoptosis. This was also valid for the subchondral bone plate [Fig. 7(b)]. In some specimens newly formed cartilage grew over the side of the hat [Fig. 7(d)].

Discussion

Focal cartilage injuries in human joints such as shoulder, hip, knee, ankle and toe, are being treated more frequently using metallic resurfacing implants[12]. The most commonly described indication for this procedure is in the symptomatic middle-aged active patient, with or without previous treatment attempts. This method can be regarded as the final attempt at joint preservation for focal joint cartilage injuries. Consequently, the salvage procedure for a failed resurfacing implant is a joint replacement, unicompartmental or total. As primary procedure joint replacement has shown inferior results for this particular patient category[22]. Despite the increasing popularity of the FKR treatment modality, there are still scarce preclinical reports such as biomechanical, finite element simulation or animal studies, to secure optimal clinical results[12].

Table II
Bone density in a 500 micron wide band adjacent to left and right sides of the implant surface

	Bone %	Marrow %
6 months		
6446 right	67.5	32.5
6446 left	63.5	36.5
7169 right	89	11
7169 left	81.4	18.6
8261 right	62.1	37.9
8261 left	71.5	28.5
Mean	***72.5***	***27.5***
1 year		
5025 right	85.7	14.3
5025 left	90.7	9.3
5040 right	72.9	27.1
5040 left	74.9	25.1
5051 right	73.8	26.2
5051 left	87.9	12.1
5067 right	63.0	37.0
5067 left	74.3	25.7
8139 right	81.0	19.0
8139 left	50.0	50.0
Mean	***75.4***	***24.6***

The main finding of this study was the excellent osseointegration of the FKR implants sealing femoral cartilage defects in sheep, and that ingrowth was not impaired over time when comparing 6–12 month postoperative data. The 90% bone ingrowth contact area of the dual coated implant is in fact high when compared to any human or animal data[11,14,15,23]. Our results confirm the hypothesis that a combination of HA on top of titanium provides complimentary benefits; HA results in fast and reliable ongrowth of bone for secure biological fixation that sustains postoperative weight-bearing, and the layer of titanium secures secondary fixation should the HA dissolve. To our best knowledge this is the first report of this double coating on a Co-Cr implant.

The slender monobloc FKR implant design was chosen in order to integrate several functions. Bone loss should be minimized while still obtaining anchorage for immediate weight-bearing. Corrosive processes were thought to be avoided if one core material only could be shaped into both the articulating surface and the anchoring peg of the implant. We chose the strong Co-Cr alloy that has worked well in human arthroplasties for several decades providing sufficient materials strength. Confirming this, we did not encounter any implant breakdown in the peg–hat section or elsewhere. Co-Cr implants, however, have no osseointegrative capacity, and are typically cemented into cancellous or cortical bone. Uncemented osseointegrated dental implants made of titanium have proven to function excellently, when a bone anchor is left unloaded for ingrowth and then tooth implants are mounted subsequently when osseointegration has occurred[24]. Unlike the biomechanical environment of the teeth, the human knee joint must preferably not be left unloaded during the postoperative healing phase for optimal rehabilitation. Orthopaedic joint implants coated with HA provide consistent biologic anchorage by osseointegration that allows early weight-bearing[25–27]. We therefore plasma-sprayed the Co-Cr alloy, first with a pure titanium layer and then with an HA coating in order to obtain a secure osseointegration of these small implants.

Hydroxyapatite supplementation to achieve bonding between implant and bone has been used in orthopaedics during the last 20 years. These calcium apatite compounds span a continuum ranging from pure HA through a varying degree of mixture with tricalcium phosphate (TCP) to pure TCP. The more TCP there is, the easier the

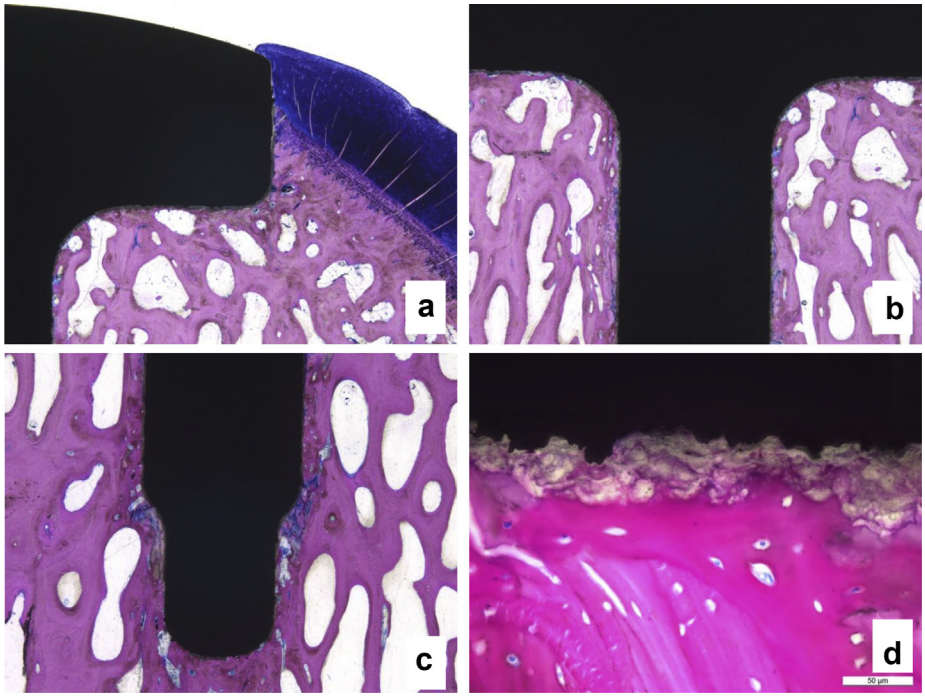

Fig. 4. Ground sections of a 12-month specimen demonstrating the osseointegration at both, the side of the hat (a), below the hat (b) and around the stem (c). Note the intimate contact between bone and the HA coating and the integrity of the latter (d).

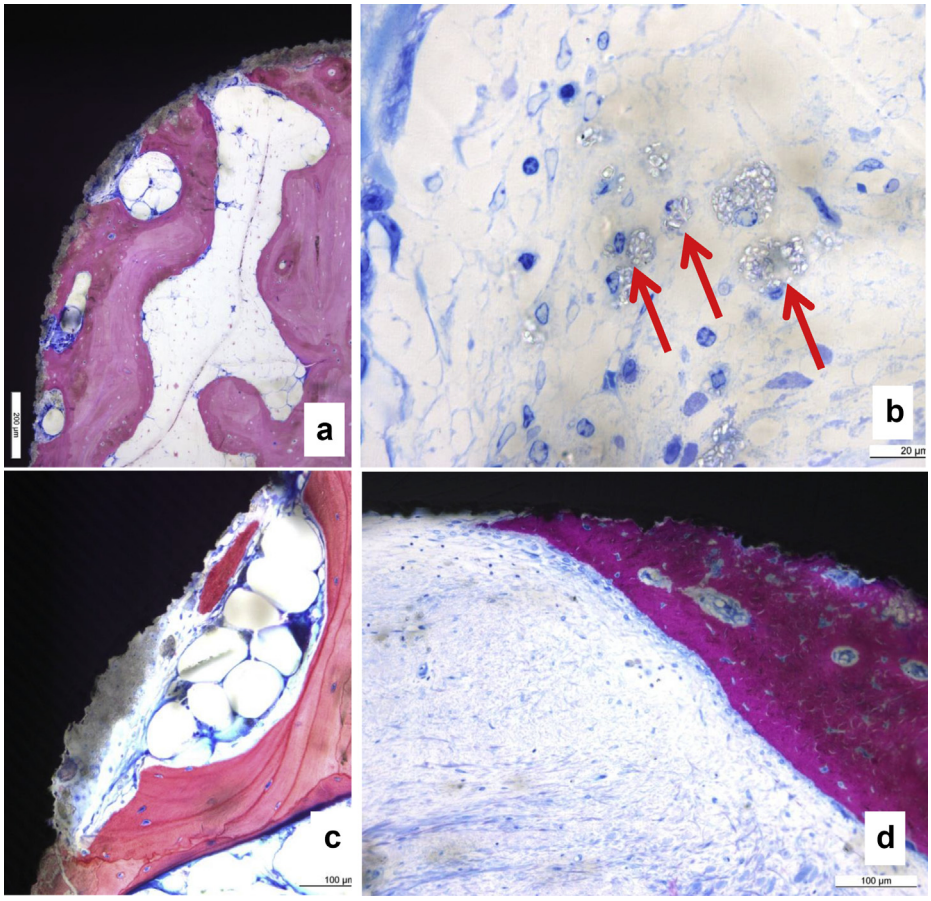

Fig. 5. Ground sections of the same 12-month specimen demonstrating the disintegration of the HA layer when exposed to bone marrow (a). HA particles were found scattered in the bone marrow chambers next to the implant surface. The HA particles were engulfed by macrophages phagocytizing the particles. Note the absence of any inflammatory reaction in the marrow (b). Completely exposed titanium sprayed implant surface area (c). Ongoing new bone formation directly along the exposed titanium layer by contact osteogenesis (d).

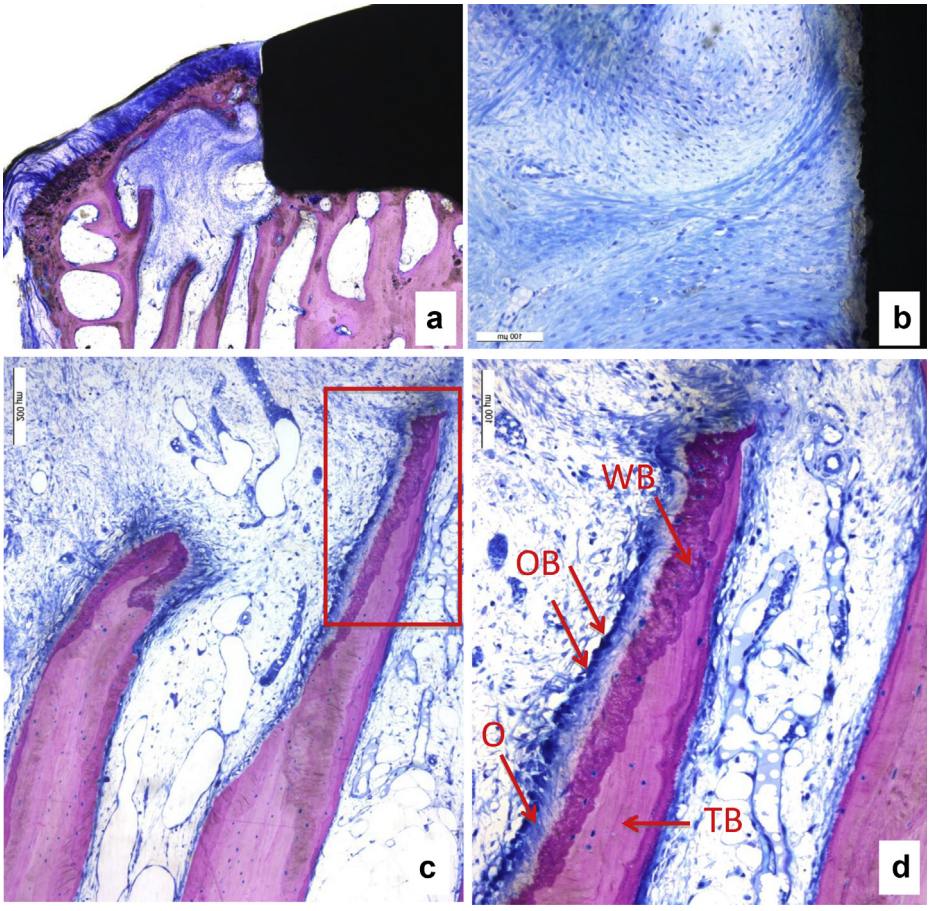

Fig. 6. Ground section showing an osteolytic area at the side of the hat (a). The area is filled with an inflammatory free connective tissue (CT in b). Native trabecular bone (TB) framing the defect shows areas of new bone formation (c, red box), characterized by the presence of osteoblasts (OB) an osteoid (O). Newly formed woven bone (WB) can clearly be distinguished by its darker stain from native trabecular bone (d, higher magnification from area outlined in c).

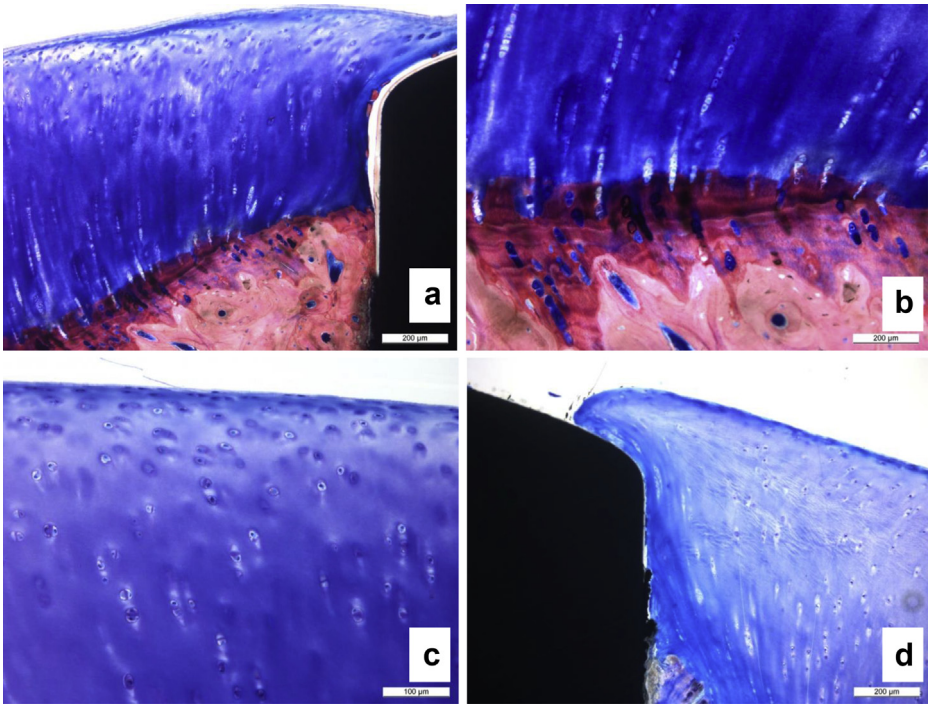

Fig. 7. Ground sections demonstrating the cartilage and its interface towards the hat. The cleft in (a) is an artefact due to the ethanol dehydration of the specimens. Note the intact subchondral bone plate in (b) healthy cartilage in (c) and the intimate cartilage adherence to the hat in (d).

compound dissolves in body fluids; however, there remains some controversy as to how stable even pure HA is[28,29]. In order to achieve best possible long-term fixation, the HA layer was hence supplemented with a coating of titanium for long-lasting osseointegration. The results of this study supported the choice of this double-coated construct; at places where bone marrow was in contact with HA, this layer tended to dissolve while the titanium layer remained intact and even showed direct bone ingrowth. Should, however a gap between bone and implant ensue, the HA was expected to fill the void securing good fixation and offering some surgical tolerance[30]. At all places along the interface, a stable bonding was manifested with no inflammatory cells or other signs of tissue reactivity.

In prosthetic surgery, the migration of wear particles with the joint fluid remains an important issue, since the related osteolysis is a known mode of fixation failure. Hence, the concept of sealing the interface between cartilage-bone and implant merits attention[26]. In the situation of a unipolar implant articulating against cartilage, wear particles are not an issue but the penetration of joint fluid is. The osteolysis adjacent to the hat seen in some of our implants might be caused by this phenomenon through an extension of the "effective joint space"[31]. In our sheep animal model the osteolytic zones did not increase or showed inflammatory reaction over time. This might confirm the sealing effect of HA which prevented the joint fluid from further penetrating the metal–bone interface. On the contrary newly formed trabeculae were seen framing these lesions also suggesting the gap-filling effect of HA as described by others[27,32]. Adaptive bone remodelling or stress shielding is another form of bone resorption that occurs more commonly adjacent to fully coated femoral implants where there is a significant mismatch in stiffness modulus at the implant–bone interface. This phenomenon is characterized by a generalized bone loss with preservation of normal bone architecture, manifested radiographically as osteopenia[33]. This was not observed in our cases as evaluated by micro-CT, histology or bone density at 1-year follow-up. In fact, bone density adjacent to the peg was always higher than in normal host bone from the same region, further suggesting the absence of stress shielding.

The primary aim of this study was to analyse osseointegration and not to draw definite conclusions regarding the joint cartilage health. Nevertheless, we did not observe gross signs of cartilage damage of the opposing tibia. This was in accordance with our previous study suggesting that the implant might have negligible effect on the opposing cartilage provided accurate position is achieved[13]. Interestingly, we also noted signs of adherence between the cartilage and the HA-covered lower circumferential area of the hat as opposed to the upper uncovered Co-Cr area[34]. It might be speculated that not only the bone–implant interface but also the cartilage–implant interface contributes to an effective seal. Based on these findings our implants have been redesigned with HA covering the entire circumferential area of the hat.

In conclusion, we have presented a double-coated (c.p.Ti + HA) Co-Cr implant in a sheep model. A firm and consistent bond to bone under weight-bearing conditions was shown. Furthermore a possible bond between HA and cartilage was observed.

Contributions of authors

NM-C: Study design, performance of all surgeries, data analyses and writing of the manuscript, HB: data analyses and writing manuscript, PS: histological preparations, data analyses, HN-S: performance of all surgeries and care of animals, LR: study design, performance of most surgeries and writing of the manuscript and A-SL: performance of most surgeries, care of animals, writing part of the manuscript. All authors: review of the manuscript.

Disclosure

Dr Martinez-Carranza reports grants from Stockholm County Council and Karolinska Institutet, grants from Karolinska University Hospital, grants from Episurf Medical AB, Stockholm, Sweden during the conduct of the study. Dr Berg reports grants from Stockholm County Council and Karolinska Institutet, grants from Episurf Medical AB, Stockholm, during the conduct of the study.
Dr Lagerstedt and Dr Nurmi-Sandh report non-financial support for laboratory facilities from Episurf Medical AB, Stockholm, during the conduct of the study. Dr Schupbach reports non-financial support for laboratory facilities from Episurf Medical AB, Stockholm during the conduct of the study.

Conflicts of interests

Dr Ryd reports financial support as a board member from Episurf Medical AB, Stockholm. For this reason he did not participate in the analysis of data.

Acknowledgement

Implants and instruments were kindly provided by Episurf Medical AB, Stockholm.

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