Different patterns of bone fixation with hydroxyapatite and resorbable CaP coatings in the rabbit tibia at 6, 12, and 52 weeks

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Received 16 September 2010; revised 30 March 2011; accepted 30 March 2011
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jbm.b.31866

Abstract: Applying bioactive coatings on orthopedic implants can increase the fixation and long-term implant survival. In our study, we compared a resorbable electrochemically deposited calcium phosphate coating (Bonit®) to a thin (40 μm) plasma-sprayed hydroxyapatite (HA) coating, applied on grit-blasted screw-shaped Ti-6Al-4V implants in the cortical region of rabbit tibia, implanted for 6, 12, and 52 weeks. The removal torque results demonstrated stronger bone-to-implant fixation for the HA than Bonit-coated screws at 6 and 12 weeks. After 52 weeks, the fixation was in favor of the Bonit-coated screws, but the difference was statistically insignificant. Coat flaking and delamination of the HA with multinucleated giant cell activity and bone resorption observed histologically seemed to preclude any significant increase in fixation comparing the HA implants at 6 versus 12 weeks and 12 versus 52 weeks. The Bonit-coated implants exhibited increasing fixation from 6 to 12 weeks and from 12 to 52 weeks, and the coat was resorbed within 6 weeks, with minimal activity of multinucleated giant cells or bone resorption. A different fixation pattern was observed for the two coatings with a sharper but time limited increase in fixation for the HA-coated screws, and a slower but more steadily increasing fixation pattern for the Bonit-coated screws. The side effects were more serious for the HA coating and limiting the expected increase in fixation with time. © 2011 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 00B: 000–000, 2011.

Key Words: Bonit, hydroxyapatite, removal torque, titanium alloy, resorbable calcium phosphate

INTRODUCTION

Enhancement of bone ingrowth prolongs the survival of orthopedic and dental implants. Bonit® is claimed to be a resorbable electrochemically deposited calcium (Ca) phosphate (P) coating, which has demonstrated promising *in vitro* results of osteoblast activation[1] and *in vivo* bone-conducting properties.[2] In a rabbit model, we observed improved histormorphometrical data and greater biomechanical forces were needed to loosen the Bonit screws compared with blasted Ti-6Al-4V implants.[3] Hydroxyapatite (HA) is widely used as a plasma-sprayed coating on implants, and it has shown strong osteoconductive properties.[4] Concern has risen over the long-term effects of HA, especially third body wear in the articulation and osteolysis possibly leading to loosening of the implant.[5] HA coatings on orthopedic devices are often thick (>150 μm). Thinner plasma-sprayed coatings can now be applied with a thickness down to 40 μm to reduce side effects. The aim of this study was to compare the biomechanical fixation and quantitative histology of Ti-6Al-4V implants coated with HA or Bonit in a rabbit model at various times of follow-up.

MATERIALS AND METHODS

Implants

Screw-shaped implants [3.75 mm in outer diameter, 3.45 mm in mean diameter (used for shear calculations, see later), 8-mm long; 6-mm treaded, with a pitch height of 0.6 mm and 2-mm square headed] were prepared by turning from rods of Ti-6Al-4V (Edstraco AB, Stockholm, Sweden). After ultrasonically degreasing in trichloroethylene and rinsing (twice) in absolute ethanol, the screws were blasted with Al_2O_3 particles of a size of 50–75 μm in a custom-mode motorized rotation chamber (ELOS Medical AB, Timmersdala, Sweden). Half the batch received a 15 ± 5-μm coating of Bonit (DOT Medical-Solutions Laboratories GmbH, Rostock, Germany). The coating was electrochemically applied at room temperature in an aqueous solution of calcium and dihydrogenphosphate salts. The Ca/P ratio was

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Contract grant sponsors: Orthopaedic Department, Rikshospitalet, The Sophies Minde Foundation, The Aase Bye and Trygve J. B. Hoffs Fond for Medical Scientific Research, Adlerbert Research Foundation, Wilhelm, Martina Research Foundation, Hjalmar Svensson Research Foundation

1.1 ± 0.1 according to the manufacturer. The other half of the batch received a standardized plasma-sprayed coating of HA (MedicalGroup, Lyon, France) with a mean thickness of 40 μm, a crystallinity of >60%, and a Ca/P ratio of 1.67–1.76 according to the manufacturer. The coating of HA covered only one side of the screw thread as shown in Figure 4. All screws were finally sterilized by gamma radiation at the respective coating company.

Surface characterization

Surface chemical analysis was performed on one unused Bonit and one HA screw using X-ray Photoelectron Spectroscopy (Physical Electronics Inc., (PHI5500) Chanhassen, Minnesota).

Surface roughness was characterized by an interferometer (MicroXam TM®, Phase-Shift, Tucson, Arizona) giving a three-dimensional evaluation of the surface. Three unused HA and three Bonit-coated implants were measured on nine sites each (three thread peaks, three valleys, and three flank areas). Each measured area was 264 × 200 μm. Three surface parameters were described[6]: S_a is a pure height descriptive parameter measuring the average height deviation in micrometers. S_{ds} = Density of summits/square micrometer is a complete spatial descriptive parameter describing how close the individual irregularities are. S_{dr} expresses in percent, the developed surface area compared with an equally sized absolute flat reference area. This parameter, influenced by variations in height and in spatial direction, is therefore called a hybrid parameter.

Scanning electron microscope (SEM, LEO 1550 Geminy, Oberkochen, Germany) was used to qualitatively investigate the sample surfaces of one Bonit screw and one HA screw.

Animals and anesthesia

The animal study was approved by the animal ethics committee at Oslo University Hospital, Rikshospitalet (33/05). Thirty female New Zealand White rabbits average 9 (range 8.5–9.5) months of age, mean weight 3.92 (standard deviation = 0.33) kg were given standard food and water, and they were kept in separate cages during the experiment period. The rabbits were anesthetized by an intramuscular injection of phentanyl/fluanizon (Hypnorm®, Vet. Janssen, Saunderton, England) at a dose of 0.5 mL/kg, and 2.5 mg diazepam (Stetsolid®, Dumex, Copenhagen, Denmark) intraperitoneally, continued peroperatively when needed. Postoperative buprenorfin 0.25 mg/kg (Temgesic®, Reckitt Benckiser, Slough, Great Britain) was administrated as analgesic. All animals were given antibiotic prophylaxis with trimetoprim 40 mg/mL; sulfamethoxazol 200 mg/mL (Borgal®, Intervet International B.V, Boxmeer, the Netherland); 0.5 mL/kg subcutaneously, which continued for 5 days with 0.2 mL/kg × 2 in the drinking water.

The hind legs were shaved and injected with local anesthesia 1 mL 0.5% lidocain (Xylocain®, AstraZeneca AB, Sødertälje, Sweden) in the operating field. The skin and fascial layers were opened under sterile conditions and closed in separate layers. The periosteum was gently pulled away, followed by low rotary drilling with three graded series of drills during profuse saline cooling, the final drill bit corresponding to the core diameter of the screw (=2.55 mm). Finally, a tap matching exactly the outer diameter of the screw was used. All instruments were tailor made. One Bonit implant and one HA implant were placed in the proximal cortical region of the medial facet of the tibia, close to the tibial tuberosities (penetrating one cortical layer and extending into the marrow cavity); Bonit implants in one leg, HA in the other. The effect on the cortical bone of the two coatings was the objective of this experiment, and the implants were positioned below the cancellous proximal region of the tibia. Follow-up time was scheduled to 6, 12, and 52 weeks (10 rabbits in each group). One rabbit in the 12-week group did not recover after surgery and died after 10 days, and one rabbit in the 52-week group was found dead after 40 weeks. The remaining 10 rabbits in the 6-week group and 9 in the 12- and 52-week groups fared well. They were killed with an overdose of pentobarbital (Apoteksbolaget AB, Uppsala, Sweden) intravenously.

Biomechanical tests

Removal torque. We always conduct removal torque tests with the animal in full anesthesia allowing for similar conditions of sample testing. The proximal tibia was exposed as described above. The removal torque needed to loosen the Bonit and the HA-coated implants from the bone bed in vivo was measured with custom-made electronic equipment. This is roughly reflecting the interfacial shear strengths.[7]

Sample preparation and evaluation of sections

The screws were left in the bone after removal torque testing. The bone-implant complex was resected en bloc with the surrounding tissue and immersed in 4% neutral buffered formaldehyde for 1 week. Undecalcified cut and ground sections were prepared using the Exakt cutting and grinding equipment (Exakt Apparatebau, Norderstedt, Germany). All samples were divided along the long axis of the screws and sectioned in the same direction (demonstrating both the anterior and posterior side of the tibia). The samples were prepared according to the procedure described by Donath[8] and Johansson and Morberg.[9] Bulk staining with basic fuchsine added to the dehydration steps in ethanol was carried out on the 6-week samples. This technique has been referred to as a staining suitable for the observation of microcracks in the light microscope.[10] However, since we found it difficult to observe cracks, the two other groups received the routine histological staining involving 1% toluidine blue in 1% Borax solution mixed in proportions of 4:1 with 1% pyronin-G solution followed by cover slipping. A Leitz Aristoplan light microscope (Leitz Gmbh, & Co. KG, Oberkochen, Germany) was used for qualitative histology and for bone length measurements on the removal torque loosened implants. Cut and ground sections of one unused Bonit screw and HA screw as well as one Bonit implant and HA implant from a dead rabbit (which was operated like the others and removal torque tested immediately afterward) were also examined in the microscope for evaluation of the coating and for its stability/endurance after the surgical procedure with screwing and removal torque testing.

Bone lengths and shear strength. A rough estimation of the shear strength could be calculated by using the removal torque and bone length measurements from one central cut and ground section only of each removal torque loosened implant. The bone length was measured using the 4× ocular magnifier. The microscope is connected to a computer using the Leitz Microvid (Ernst Leitz Wetzlar GMBH, Germany) unit. The microscope oculars are calibrated using a known scale with the aid of the computer program, and the bone lengths are measured in millimeter and reported with two decimals.

We examined the length of bone in close contact with the implant through the cortical region on the original ground specimen. The soft tissue regions in the cortical regions were excluded. The bone marrow was without spongious bone in this part of the tibia, visualized on Figures 5(b) and 7(b). The formula: $T/\pi \times d \times \mathrm{rl} \times l$ was applied, where T = removal torque (Ncm), d = mean diameter of the implant (3.45 mm), rl = lever arm (= radius, i.e., 1.725 mm), and l = the entire bone tissue length along the implant surface (mm) in the cortical region.[11] The measurement is a reflection of the shear strength between implant and bone.[12,13]

Statistical analyses

The measured parameters exhibited a normal distribution demonstrated by the q–q plot. Student t-test was used for intraindividual comparisons. For interindividual comparisons, an independent t-test was used and adjusted for Bonferroni. An * is given for the Bonferroni corrected p values in the Results section. Confidence intervals (CIs) are given for the comparisons, and p values < 0.05 are considered statistically significant. The statistical program SPSS® version 16.0 for Windows® was used.

RESULTS

Surface characterization

Surface chemical composition. The surface of both implants comprised calcium, phosphorous, oxygen, and carbon. The HA-coated implants also revealed traces of zinc and nitrogen.

Surface roughness. The S_a and S_{dr} parameters were significantly higher for the HA than the Bonit screws. The density of summits (Table I) was significantly greater on the Bonit surface due to the spiky appearance as demonstrated with SEM (Figures 1 and 2).

TABLE I. Surface Roughness

	Bonit	HA	*p*
S_a (μm)	1.51 (0.15)	3.04 (0.54)	<0.001
S_{ds} (ds/μm^2)	0.138 (0.01)	0.107 (0.01)	<0.001
S_{dr} (%)	102.93 (14.08)	165.29 (44.98)	<0.001

Data are given as mean (standard deviation).

FIGURE 1. SEM of an used Bonit-coated surface.

Light microscopical investigation of the sections from the unused screws (cut and ground in the similar manner as the bone-implant samples) demonstrated the appearance of the coating on both screws. The microscopic picture is taken from middle section of the threaded part of the screws (Figures 3 and 4). The Bonit sample showed black particles in the evenly distributed coating layer. The HA coating was unequally distributed with variations in thickness. The coating was consistently found on the same flank side of the thread, diminishing toward the other; the latter probably being "leeward" during the plasma-spraying process.

Microscopical evaluation of the baseline screws demonstrated persistent coatings on both samples after insertion and removal torque testing.

Biomechanical results. The HA screws demonstrated a strong fixation at 6 weeks, moderately increasing to 12 weeks, without further enhanced fixation at 52 weeks, while the Bonit-coated screws exhibited increasing fixation with

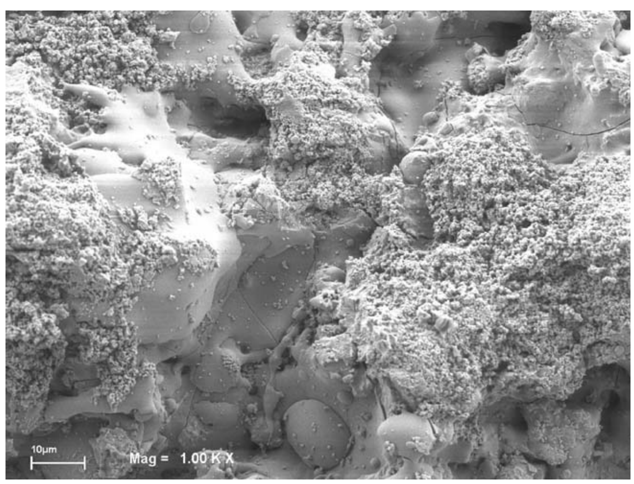

FIGURE 2. SEM of an used HA-coated surface. The coating is covering only one side of the thread.

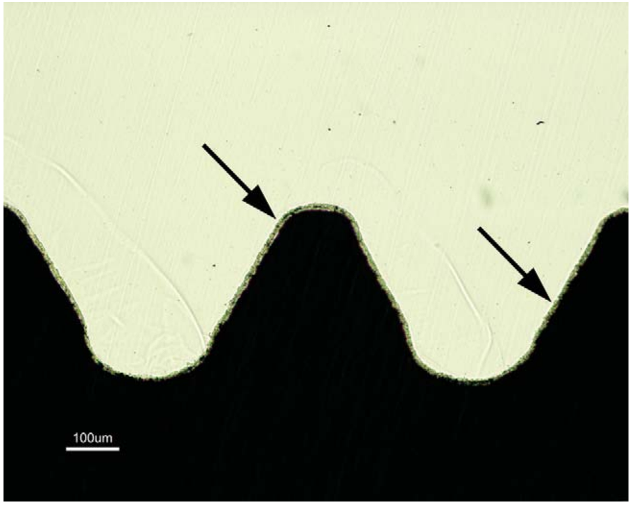

FIGURE 3. Light microscopy of a cut and ground section from the unused Bonit screw. The uniformly distributed coating is grayish with black particles (indicated with black arrows).[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

time. The fixation was in favor of HA after 6 and 12 weeks compared with Bonit, whereas the opposite was the case after 52 weeks; however, the latter was not statistically significant (Table II).

The increased fixation of Bonit at 6 vs. 12 weeks and 12 vs. 52 weeks was statistically significant ($p = 0.005$* and $p = 0.004$*, respectively). The increased fixation of HA was insignificant between the 6 vs. 12 weeks and 12 vs. 52 weeks ($p = 0.5$* and $p = 1.0$*, respectively).

Bone length and shear strength. The two coatings exhibited different patterns of bone length and shear strength

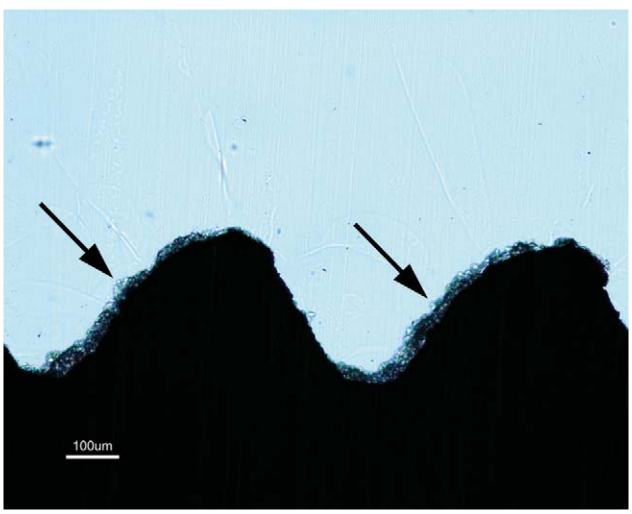

FIGURE 4. Light microscopy of a cut and ground section from the unused HA screw. The coating is absent from one flank of the thread. The same pattern was seen on all the screws evaluated *in situ* after implantation (arrows indicate the coating). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Removal Torque in Newtoncentimeter

	Bonit	HA	*p*
6 weeks ($n = 10$)	45.0 ± 11.9	79.8 ± 19.3	0.005
12 weeks ($n = 9$)	70.4 ± 12.8	92.5 ± 27.5	0.028
52 weeks ($n = 9$)	109.8 ± 30.0	93.9 ± 34.5	0.086

Data are given as mean values ± standard deviations.

values with increasing time. A uniform picture was found for the Bonit-coated implants demonstrating a steady increase in removal torque (more) and bone length (less) with time giving correspondently enhanced shear strength throughout the follow-up. The HA screws demonstrated its greatest bone length at 12 weeks, whereas the removal torque exhibited a minimal increase with time thus giving shear strength peak at 6 and 52 weeks. The bone length was 65% and 61% greater for the Bonit compared with the HA screws at 6 and 52 weeks, respectively; at 12 weeks, the bone length was approximately similar. The difference in bone lengths adjacent to the Bonit-coated implants compared with HA resulted in 300% higher shear strength in favor of the HA screws at 6 weeks (p = 0.005) (Tables III and IV).

Histologic examination. The Bonit screws exhibited a uniform pattern of loosening between implant and bone after application of the removal torque. Coating remnants were not observed in the interface region when inspected in the light microscope at any observation time. Callus formation (i.e., periosteal bone tissue formation) and immature young bone were observed at 6 weeks, maturing through 12 weeks with remodeling and conversion to a lamellar structure after 52 weeks. The bone-implant length increased gradually. Multinucleated giant cells and macrophages were seen occasionally in the interface region. The overall histological picture revealed a "calm" normal bone remodeling impression [Figures 5 (a–c) and 6].

The HA–implant interface revealed detachment both between the bulk implant and coating (HA adherent to the bone) as well as between the HA coating and bone (HA adherent to the implant), both patterns being demonstrated along the very same implant at all times of follow-up. When blood was seen in the interface between the coat and bone/implant, the detachment probably occurred during the removal torque test. Detachment was not seen through the coating or through the bone outside the coating.

The bone in the vicinity of the HA-coated screws demonstrated a less uniform picture as compared with the Bonit implants. At 6 weeks, immature young bone was observed

TABLE III. Bone Length in Millimeter

	Bonit	HA	*p*
6 weeks ($n = 10$)	2.72 (0.42)	1.76 (0.75)	0.011
12 weeks ($n = 9$)	3.05 (0.73)	3.14 (1.24)	0.374
52 weeks ($n = 9$)	3.16 (0.85)	1.93 (0.76)	0.038

Data are given as mean values (standard deviation).

TABLE IV. Mean (Standard Deviation) Shear Strength Values in Square Newtonmillimeter

	Bonit	HA	p
6 weeks ($n = 10$)	9.01 (2.57)	29.13 (14.91)	0.005
12 weeks ($n = 9$)	12.82 (2.82)	17.08 (6.29)	0.139
52 weeks ($n = 9$)	19.74 (7.31)	36.27 (33.25)	0.214

in the contact area, as well as resorption of bone and HA. At 12 weeks, the most active histological picture was observed with remodeling of bone and resorption of HA substituted by immature bone or soft tissue in the contact zone and with remnants of HA in the vicinity. Remodeling cavities were also seen further away from the implant often containing HA particles. A similar, but less active picture was found at 52 weeks, where more resorption and substitution of HA was seen. HA was also observed in remodeling cavities further away in the bone. The larger particles where surrounded by cells, minor particles were internalized in cells. The most active and complex histological picture was seen at 12 weeks, diminishing at 52 weeks. Multinucleated giant cells were frequently observed, often containing granules of HA. The bone length was less compared with the Bonit implants at 6 and 12 weeks and approximately similar at 12 weeks [Figures 7 (a–c) and 8].

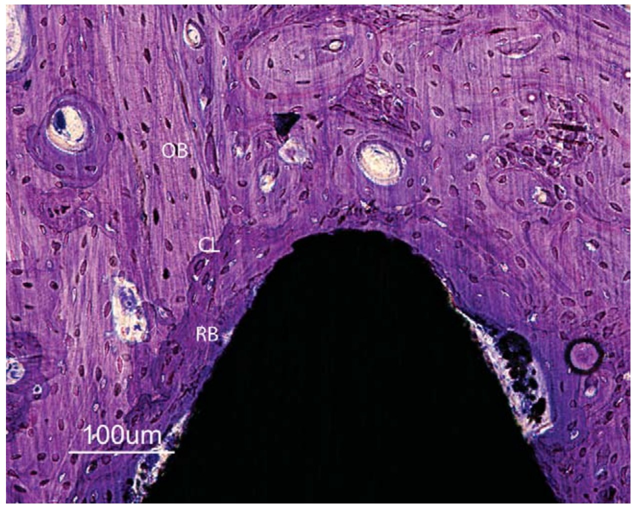

FIGURE 6. Close up of a Bonit-coated screw at 12 weeks. The entire interface region reveals remodeled bone (RB) tissue. Except macrophages being observed in the soft tissue regions in the interface no inflammatory reactions were observed. Cement lines (CL) are clearly visible between new formed bone and old cortical bone (OB). Both bone-forming and bone resorption cavities can be observed. Toluidine blue routine histological staining. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

Currently, much attention is related to characterization of implant surfaces. Albrektsson and Wennerberg[14] considered the optimal surface roughness to be $S_a \approx 1.5$ μm in an oral implants review. The surface roughness (S_a) of Bonit was more favorable (≈1.5 μm) compared with HA (≈3.0); still the early bone response was stronger for HA. The optimal S_{ds} and S_{dr} are presently not known. After 6 weeks all Bonit is resorbed evaluated microscopically, exposing the alloy surface roughness. We found the surface roughness of the same type of uncoated screws to be $S_a \approx 0.7$ μm.[3] Thus, from 6 weeks on, neither Bonit (having $S_a \approx 0.7$ μm when the coating is resorbed) nor HA (having $S_a \approx 3.0$) had an optimal roughness. A rougher or a smoother surface than $S_a \approx 1.5$ μm on titanium implants exhibited less bone ingrowth in one short- and one long-term study by Wennerberg et al.[15,16] The surface roughness of our Bonit- and HA-coated implants cannot explain the different fixation patterns.

The higher removal torque values (almost the twice of Bonit after 6 weeks) at 6 and 12 weeks in favor of HA may be attributed to stronger bioactive properties. The ability to induce early intimate contact between bone and HA-coated compared with Ti-alloy implants has been demonstrated by Soballe,[17] observing higher push-out values, more bone ingrowth, and improved gap healing up to 16 weeks in a dog model. Chang et al.[18] found superior attachment and bone-implant contact with different plasma-sprayed HA coating compared with sandblasted commercially pure titanium up to 26 weeks. The two studies did not perform any

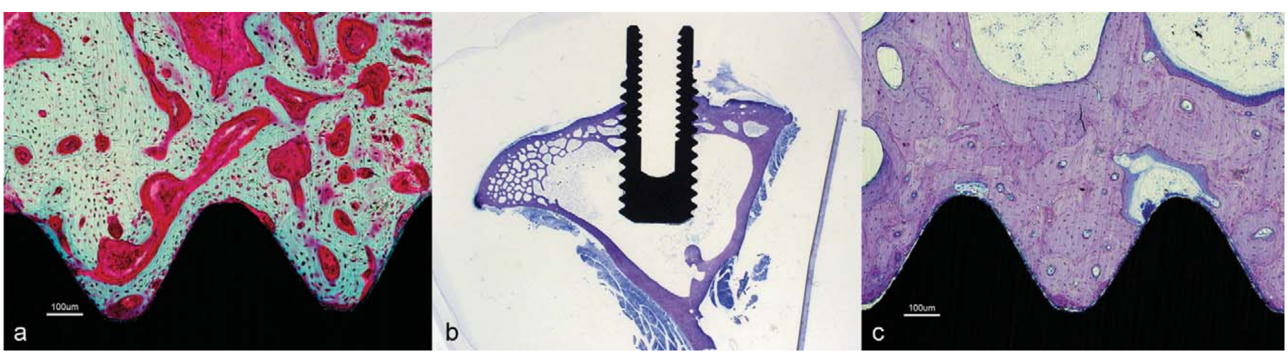

FIGURE 5. Photomicrographs of sections. (a) Six-week Bonit screw, bulk staining with basic fuchsine. (b) Overview of a 52-week sample demonstrating the shape and position of the screw and the macroscopic appearance in the tibial bone. (c) Magnification of a 52-week Bonit screw demonstrating the bone-implant contact. Toluidine blue routine histological staining in (b) and (c). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

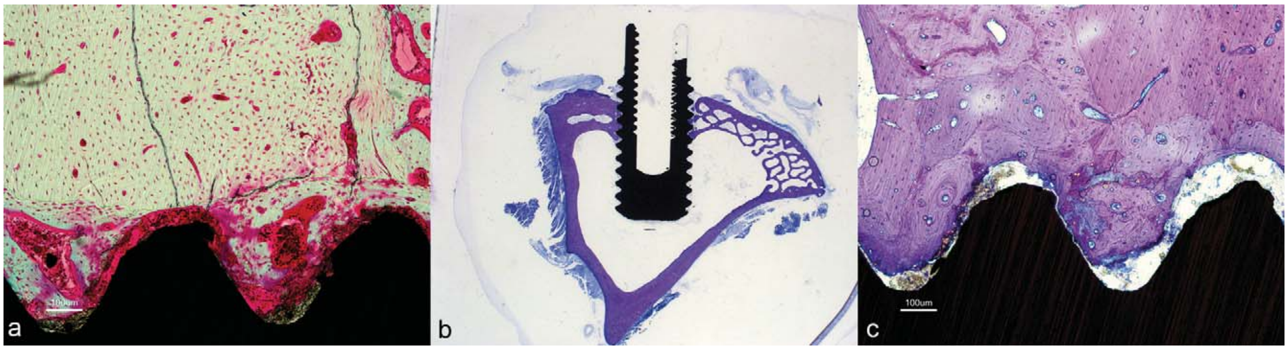

FIGURE 7. Photomicrographs of HA-coated implants: (a) 6-week bulk staining with basic fuchsine. (b) Overview of the 52-week sample demonstrating the shape and position of the screw and the macroscopic appearance. (c) Magnification of the 52-week HA screw. Toluidine blue routine histological staining in (b) and (c). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

qualitatively histological evaluation of the tissue response in the vicinity of the implants. An interaction of several factors determine whether osseointegration of an implant will take place or not; the first weeks being critical. The rapid and strong bone response to HA is important as to achieve direct bone-implant contact and is especially desired in the clinical situation with joint replacements dependent on early loading. The Bonit-coated screws exhibited a predictable but less early bioactive pattern. The bone-implant length was in favor of Bonit at 6 weeks compared with HA, but the interface bonding was weaker (lower removal torque and shear strength). The significance of the lack of HA on one side of the thread is difficult to estimate. The discontinuity of the HA might weaken the bond between the implant and coating and increase the deflaking tendency. We found persistent coating on the baseline test implants after screwing in and removal torque testing, at least exhibiting shear resistance of the coat. Whether a continuous coat would have increased the fixation or increased the side effects remains unanswered, but it demonstrates the difficulties in the application of thin plasma-sprayed coatings. Long-term negative effects of HA have been reported in experimental and clinical studies[19,20] with delamination and flaking of the coating, foreign body inflammation, and implant loosening. Morscher et al. experienced excellent short-term results with a thick HA-coated hip arthroplasty, but these results deteriorated after longer observation. Ten of 25 revisions were due to severe osteolysis in the acetabulum and the proximal femur. HA was found in the articulating surface (embedded in the polyethylene and scratching the chrome-cobalt head) as well as in the granulomatous tissue in the osteolytic areas, demonstrated with SEM and energy-dispersive X-ray microanalysis.[21] Histological examinations were not performed. An *in vitro* study by Velard et al.[22] found polymorph nuclear response as well as proinflammatory mediators to HA particles, postulated to contribute to implant associated inflammation. These mechanisms could explain the undulating bone length and shear strength as well as the disorderly histological picture adjacent to the HA-coated screws. Generally, the removal torque, bone-implant length, and shear strength are expected to increase with time and loading.[7,23] Also an increase in shear strength in the bone–implant interface with time is expected due to maturization of the bone with resorption of callus and woven bone and conversion to a stronger lamellar bone structure.[23] For the HA-coated screws, this process subsided after 12 weeks in regard to the removal torque and the bone length, although the interfacial fixation of the intact bone-implant areas still remained strong. This is consistent with the histological picture of the HA screws with flaking of the coating, delamination, and multinucleated giant cells. At 52 weeks, the HA bone length decreased, but more mature lamellar bone structure may give a stronger point fixation preventing a reduced removal torque. The new thin plasma-sprayed HA coating used in our study exhibited a bony reaction similar to the more widely used thicker coatings, but less volume of HA on our implants may have limited the inflammatory soft tissue response, and the

FIGURE 8. A 12-week close up of a HA-coated implant demonstrating loose HA particles (arrows) in the soft tissue outside thread peak as well as in bone remodeling cavities further away from the implant. Older cortical bone can be observed separated from younger bone by cement lines. Note regions of more woven bone (immature) structure internalized in the remodeled bone. OB, old bone; WB, woven bone; and CL, cement lines. Toluidine blue routine histological staining. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

resorption of much HA at 52 weeks can explain the less active histological picture as compared with the 12-week samples. At the intact interface between bone and HA, the point fixation was stronger for the HA at all observation periods but statistically significant only at 6 weeks. We attribute this difference to the stronger bioactivity and bone-stimulating effect of plasma-sprayed HA. Potential side-effects of HA coatings should be considered when choosing surface modifications on clinical orthopedic and dental implants.

A steady increase in the bone length and the removal torque of the Bonit-coated screws was seen during the observation period. The resorption of Bonit after 3–6 weeks resulted in direct bone–metal contact and probably constituted a stable situation.[3] The histological picture with bone remodeling into a lamellar structure and minimal inflammatory response probably increases implant stability. A similar picture has been demonstrated in long-term studies of blasted titanium and titanium-alloy implants in the same animal model as well as in clinical and retrieval studies of humans.[7,24,25] Our results suggest Bonit to represent a true resorbable calcium phosphate coating, transforming the interface into direct bone–implant contact resembling the fixation of titanium-alloy implants. No indication of any side effect of the coating has been demonstrated. Apart from our former investigation,[3] there are no *in vivo* or clinical publications involving Bonit.

ACKNOWLEDGMENTS

We thank M. Vardal, Statistician, Department of Biostatistics, Rikshospitalet/University of Oslo for valuable help with the statistical methods. No benefits have been received or will be received from a commercial party related directly or indirectly to the subject of this article by any of the authors.

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