Bone remodelling and migration after insertion of femoral stems with different surface coatings. Clinical and experimental studies

Thesis

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En kvinne som ønsker å nå toppen, må se ut som en ung pike, oppføre seg som en kvinne, tenke som en mann og arbeide som en hest

Abbreviations

μM Micrometer

AP Anterior-posterior

BM Bonemaster®

BMD Bone mineral density

BSP Bone sialoprotein

CI Confidence Interval

CV Coefficient of Variation

DH Diakonhjemmet Hospital

DXA Dual-energy X-ray absorptiometry

EDHA Electrochemically Deposited Hydroxy Apatite

EM Electron microscope

HA Hydroxy Apatite

HHS Harris Hip Score

MPa Mega Pascal

OA Osteoarthritis

OUS Oslo University Hospital

RCT Randomized Controlled Trial

RSA Radiostereometric analysis

THA Total Hip Arthroplasty

Ti Titanium

ACKNOWLEDGMENTS

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LIST OF PAPERS

Paper 1.

Bøe B, Heier T, Nordsletten L: Measurement of early bone loss around an uncemented femoral stem. Acta Orthop 2011; 82:321-324.

Paper 2.

Bøe B, Röhrl SM, Heier T, Snorrason F, Nordsletten L: A prospective randomized study comparing electrochemically deposited hydroxyapatite and plasma-sprayed hydroxyapatite on titanium stems. Acta Orthop 2011; 82:13-19.

Paper 3

Bøe B, Solberg LB, Støen RØ, Reinholt FP, Ellingsen JE, Nordsletten L: Osteoinduction by implantation of titanium discs with two different hydroxyapatite coatings in rabbit muscles. Submitted.

1. INTRODUCTION

1.1 Total hip arthroplasty (THA)

The original intent of the operation called arthroplasty was to restore motion to an ankylosed joint (1). However, while a resection restores motion, an arthroplasty, to be successful, must not only restore motion but also provide stability of the joint, a crucial difference. Historically, different surgeons used a wide variety of materials. As early as 1927, Hey-Groves had replaced the head of the femur of a patient using a prosthesis made of ivory (2). In the 1930's Marius Nygaard Smith-Petersen had success with acetabular cups made of vitallium, the first non-reactive metal alloy to be used in orthopaedic surgery. In 1949 the Judet brothers in France reported their experience with the use of an acrylic-stemmed prosthesis in 76 patients undergoing arthroplasty (3). The acrylic prosthesis was quickly introduced in the treatment of fresh intracapsular hip fractures. With hemiarthroplasties becoming popular for the treatment of intracapsular hip fractures, it was logical to expand the operation to include an acetabular component. The most sophisticated interposition arthroplasty procedure was devised by Bateman who developed the bipolar prosthesis that provided two planes of motion (4).

The modern era of total hip arthroplasty (THA) started with Sir John Charnley's introduction of a low friction arthroplasty (5). He adopted the possibility of using cement for fixation (6) and led the way in establishing a useful procedure that could be performed by any well-trained orthopaedic

surgeon. The long-term clinical results of the Charnley THA make this prosthesis the “gold standard” of hip replacement, to which innovations have to be compared (7, 8). Charnley not only developed the low friction arthroplasty, but also the whole concept of performing hip replacement surgery, including the sterile-air operating theatre enclosure (9).

In the 1970s, it became clear that cemented fixation had limitations, particularly in young active male patients (10). This indicated that other methods than using cement for implant fixation could be appropriate in certain groups of patients. A more biological fixation was sought, reintroducing the cementless concept and leading to the development of several cementless stems. Early versions, such as Anatomic Medullary Locking (AML) and the Lord prosthesis had relatively long stems, which were entirely coated or textured to achieve initial stability and secondary bone ingrowth. Even though some of these implants turned out to be well fixed (11, 12), there were problems with proximal bone loss, thigh pain and difficult extraction at revision. Further development led to shorter stems with proximal porous coatings consisting of sintered beads. The results of these types of designs, however, were inferior to those with the cemented THA (13-15). The cementless technique relied on biological fixation provided by initial stability, followed by bone ingrowth into a textured or porous implant surface (16, 17). To improve the biological fixation ceramic coatings were introduced. First, de Groot published results of plasma sprayed hydroxyapatite (HA) coated implants in animals in 1987 (18). He found that HA had osteoconductive properties and that HA coated implants gave better mechanical fixation than uncoated implants under optimal surgical conditions. In studies with dogs, Søballe

showed enhanced bone ingrowth and mechanical stability in a gap situation during non-weight bearing and weight-bearing conditions, as well as under stable and unstable conditions (19-23).

Although the use of hydroxyapatite is common in clinics, there are not many randomized controlled trials comparing outcomes (24-26). Some studies reviewing clinical results, x-ray findings, and revision rates have been unable to find a significant difference between hydroxyapatite and non–hydroxyapatite-coated stems (27-29). However, other studies have suggested an advantage to hydroxyapatite-coated components through an earlier return to activity, decreased thigh pain, less subsidence with radiostereometric analysis (RSA) and fewer radiolucent lines (30-33). Palm et al found a significant higher revision rate in their non-hydroxyapatite group at 8 to 10 years in a small number of patients (n=20) (34).

Electrochemical deposited hydroxyapatite (EDHA) has been introduced as a possible implant coating recent years. In animal studies EDHA coating has contributed to fixation between implant and bone. EDHA results in different surface morphology, with higher surface area, and appears to result in better mechanical integration of coating and mineralized tissue (35).

Today, THA is regarded one of the most successful surgical procedures in orthopaedics usually increasing quality of life with excellent hip function and pain relief. In Norway there are more than 6000 hip reconstructions per year (36).

1.2 Cementless fixation

Fixation of hip implants is still an issue to consider. Orthopaedic surgeons have to choose between cemented and cementless implants. Cemented implants revolutionized arthroplasty surgery in the 60's. However, long-term results were variable, especially in young active patients, and cementless implants were re-introduced. Cementless fixation aims to preserve host bone to allow for ease of revision and, most importantly, to provide lasting fixation and a living interface without cement. Many different modes of cementless fixation have been clinically tested in patients. Various stem geometry and surface properties are commonly used. There is tapered, anatomical, custom made, rectangular cross-section and quite dissimilar stem designs that have proven good results (37-39). Clinical experience over the last decades with proximally and extensively micro porous coated stems, has led to continued interest. The porous surface, sometimes supplied by a bioactive ceramic top coating, enhances bone ingrowth and biological fixation (40). However, other implants with varying surface roughness, from the very rough Lord prosthesis (madreporic) to Zweymuller and CLS, roughened by sandblasting with corundum (a fine sand made of aluminium oxide), have shown good results after more than 10 years (12, 41-44). Acid etching is another way to roughen the implant surface for macro interlock with bone (45). Most designs restrict coatings to the proximal part of the stem. Distally they have polished or satin finish to avoid distal bony fixation leading to proximal stress shielding and difficult revisions.

Cementless THA is becoming increasingly popular and is now the preferred choice of many orthopaedic surgeons worldwide in any patient category. In the Scandinavian Arthroplasty registers the results of cementless THA have

been generally inferior to the well-documented cemented THA (46-49). Danish orthopaedic surgeons are, according to their register, using more cementless implants then surgeons in Norway and Sweden (50, 51). The number of cementless implants might be the reason why Denmark has a higher revision rate than Norway and Sweden (50). Wear and osteolysis, which were blamed on the cement in the 1980's, are problems of even greater magnitude in cementless hip arthroplasty. Osteolysis and loose HA-particles have been observed extended around HA coated acetabular components (52, 53). In order to address the problem new bearings have been developed.

1.3 Implant surface

Stainless steel, cobalt-chromium alloys and titanium alloys are commonly used as stem material in orthopaedic surgery. Initially stainless steel was not strong enough to prevent stem fractures. Later developments included improving alloy purity and a process of cold working (rolling and compression) that increases strength. Cobalt chrome alloys were preferred because of high strength and hardness. Its high corrosion and wear resistance made it suitable for bearings as well. Titanium implants have shown convincing biocompatibility (54, 55), although there are papers concluding that modern implant metals cause a uniform bone reaction (56). However, inferior mechanical properties have led to the development of a titanium alloy (Ti-6Al-4V), which has superior mechanical properties. Titanium is rapidly oxidized when exposed to oxygen (57) and a stable oxide surface will exist on a titanium implant in clinical use. The tissue will then be exposed to a ceramic titanium oxide surface and not directly to the titanium metal.

The implant surface can further be polished or made porous and treated with different coatings. Porous metals have become the material of choice for biological fixation (58). The pores in “porous coating” may vary in size (150-350 microns) and porosity (approximately 30%). The theoretical concept for making this rough surface is to increase the surface area, thus providing larger contact area between implant and bone. This should anchor the implant by ingrowth of bone and result in optimal stress distribution.
Hydroxyapatite ceramic coating has been shown to enhance bone ingrowth (19) and will be further described.

1.4 Aseptic loosening

Normal bone can be cortical or cancellous. Cortical bone is compact and composed of tightly packed osteons. Intraosseus circulation provides nutrition. It has a slow turnover rate and high resistance to torsion and bending. Cancellous bone is less dense and undergoes more remodelling. It has a higher turnover rate and is more elastic than cortical bone. The bone cells are osteoblasts, which form bone, osteocytes, which maintain bone, and osteoclasts, which resorb bone. Bone mass regulation depends on several mechanisms in the host and bone mineral density (BMD) remains constant when the deposition rate equals the resorption rate, and when osteoblastic activity equals osteoclastic activity. Osteolysis refers to an active resorption of bone matrix by osteoclasts as part of an ongoing disease process. More than 30 years ago Charnley observed osteolysis around implants with subsequent loosening. He thought it was infection (59). Later, alternative explanations based on foreign body reaction theories were presented. Histological

investigations showed macrophages and particles in the joint capsule and in a fibrous layer surrounding the implant (60). Interleukin-1 is a potent stimulator of osteoclastic bone resorption and has been found in membranes surrounding loose joint implants (61). However, these findings are also reported around well fixed, non-septic stems (62). It was first thought to be a reaction to cement particles, but is now also shown around uncemented implants (63). The periprosthetic membranes are thought to arise because of damage of the bone tissue during implantation and micro-movements of the implant (64). Micro-movements also result in fibrous tissue in a bone fracture. If a fracture is totally stable it can heal via direct bone formation (65). However, if there is any movement in the fracture gap the healing process will induce fibrous tissue and chondral ossification. The fracture healing process illustrates how mechanical stability and loading conditions affect bone remodelling. Analyses of the periprosthetic membrane have shown macrophages loaded with plastic particles (66, 67), cement and metal. The particles themselves have not been found to be sufficient to cause osteolysis, but may do so in combination with fluid pressure or movement (68, 69). Particle generation is influenced by several factors including patient age, activity level, body mass index (BMI), bone quality and implant related factors. Host factors are important in eliciting wear and thereby also osteolysis (70-72). Although the understanding of the pathophysiology and of osteolysis has increased, its treatment and prevention remain challenging.

1.5 Hydroxyapatite

HA has been used since the 1980's as a coating material on cementless implants to obtain faster and better bone ingrowth (19, 73). HA is present in natural bone mineral and has the potential for direct chemical bond to the bone tissue. It has been proven to be osteoconductive, meaning that it can stimulate bone to grow to and on its surface. Partial dissolution of the apatite, and increase of the local concentration of calcium and phosphate, is likely to initiate the process. Classically, HA is applied to porous coated or grit-blasted metal surfaces of orthopaedic implants by plasma spraying. Plasma spraying means melting accelerated HA particles by injecting them into a high-temperature plasma tail flame of ionized gas under a vacuum where the HA particles solidify on the metal substrate (19). Many factors are important for the quality and behaviour of the HA coating.

- Temperature of plasma tail (1500°C)
- Chemical composition (purity 95-97%)
- Ca/P ratio (1.67)
- Crystallinity (70-90%)
- Microstructure (density)
- Adhesive strength relative to the implant (bond strength 5-65MPa)
- Thickness of coating
- Trace components

In cases where HA has been degraded, bone has been found to grow in direct contact with the metal surface. This means that long-term fixation might be

successful despite a complete degradation of the coating, especially if the surface is porous (74).

The strength of the HA coating increases with decreasing thickness. Potential negative effects are fractures and delaminating of the coating possibly leading to formation of particles that can enter the joint and cause ”third body wear” (53). Fractures are more likely to happen if the coating is thick (75). A coating thickness of 50-75 μm is recommended (23). Other general recommendations regarding HA coatings include as high a purity as possible, crystallinity of 70-90%, Ca/P ratio of 1.67 and adhesive strength between 5 MPa and 65 MPa, depending on the condition of the metal substrate. The lower the crystallinity, the quicker the HA coating is resorbed into the bone tissue (76). This is because a low crystalline coating releases more calcium and phosphate ions due to dissolution. Thinner coatings are achieved by different application methods and should decrease the fracture and delaminating risks. We have not seen increased wear of HA coated implants so far (77-79). Uncemented stems are generally performing well according to the Norwegian arthroplasty register (80). In 2007 the rate of failure because of aseptic stem loosening at 10 years follow-up, was below 4% for all stems that were still in use. However, in combination with uncemented cups the total hip survival was relatively poor (43-91%).

1.6 Electrochemically deposited hydroxyapatite (EDHA)

In the past few decades, several coating methods have been developed to deposit HA onto titanium surfaces, including plasma spraying, ion beam sputtering, sol-gel, electrophoretic deposition, and electrochemical deposition

(81-83). Of these methods, plasma spraying is the most frequently used method for coating titanium implant surfaces. However, the high temperature of the plasma spray usually decomposes the HA. Moreover, the plasma spray coating technique is not capable of producing a uniform HA coating on implants with a complex surface. In comparison, electrochemical deposition has the unique advantage of forming a uniform coating. In addition, the deposition process can be conducted at room temperature and the morphology of the coating can be controlled by varying the electrochemical potential and electrolyte concentration (84). Bonemaster® is hydroxyapatite deposited electrochemically. In **paper 2** the titanium surface underneath was porous coated (*Figure 1*). Deposition was performed in a (Ca^{++}/$HxPO_4(3-x)-$)-containing electrolyte, with near physiological conditions with regard to pH (6.4) and temperature (36°C). Cathodic alkalization leads first to the formation of a thin homogeneous layer that shows a nanoscale surface topography of alternating wall-like elevations and channels. It is thought that these channels in the calcium phosphate pre-layer form as pathways for hydroxyl ions and hydrogen. Upon this layer, spheres of amorphous calcium phosphate (ACP) form. According to transmission electron microscopy images, these spheres consist of small clusters of calcium phosphate (30 nm) and can grow up to 300 nm in diameter. High water content is characteristic of this ACP. As a function of current density, the ACP is then transformed into crystalline hydroxyapatite (HAP). The morphology of the HAP crystals can be described as needles with dimensions of <500-nm length and <60-nm width (*Figure 2*). By choice of different electrochemical parameters, a homogeneous coating of either ACP, HAP, or the intermediate phase can be achieved, thus allowing

the formation of coatings with different properties in solubility and morphology (85).

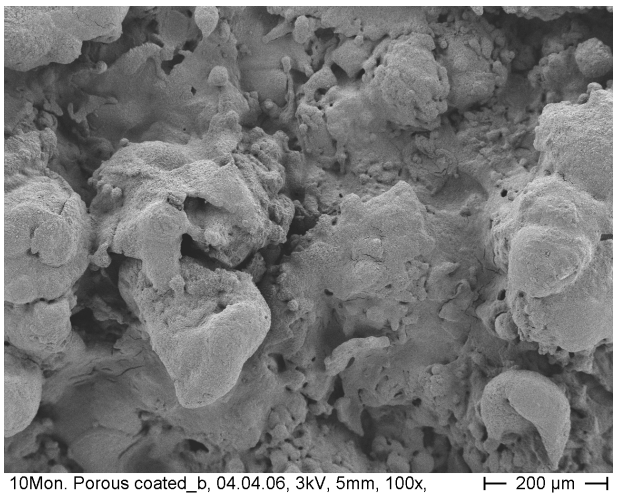

Figure 1. Titanium porous coating 100x

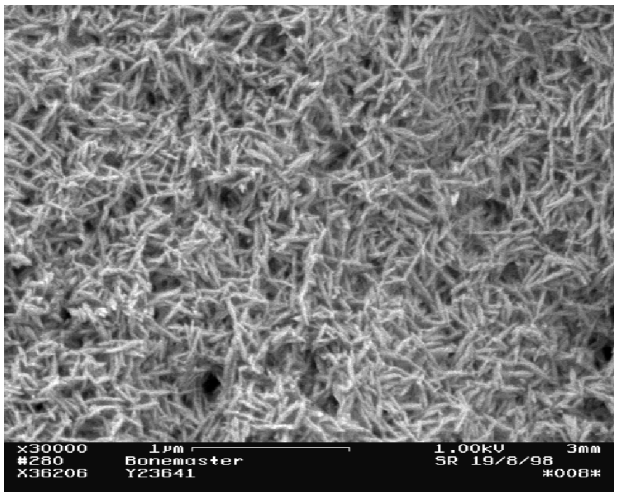

Figure 2. Bonemaster® in electron microscope (EM), 30000x

1.7 Bone remodelling

After THA there has been documented changes in bone mineral density (BMD) around the implant (37, 86-94). The typical pattern has been proximal

bone loss and distal bone increase. Especially the medial femoral cortex, the calcar area, has suffered from a decrease in BMD, which many believe is due to reduced load. This phenomenon is known as stress shielding of proximal bone (95, 96). If the bone ingrowth of a femoral stem occurs mainly in the diaphysis, the weight-bearing forces bypass the proximal femur, possibly leading to loss of bone density (97). Radiographically, increased bone density is seen surrounding the distal extent of the porous coating (but not below the tip). As a result the proximal femur is stress-shielded. With proximal porous coating, the porous surface is kept in the metaphysal and upper metadiaphysal regions of the femur. With this design concept, proximal bone ingrowth allows proximal bone loading and less stress shielding. Most of this bone remodelling occurs during the first three months (98, 99). In fact, we are not sure when bone loss starts after the operation. Results from implant studies are usually presented as changes in BMD as a function of time. The baseline and reference value for such calculations is the first measurement after the operation. The baseline measurement has been performed at different time points in different studies (90, 100). If there is rapid bone loss immediately after an operation this will influence the reference value and hence the results. After the first year bone loss may progress at a diminished rate (88), and in some cases we see a restoration of bone (101, 102). There have been different patterns of bone loss depending on whether the stem subsided or was stable (103). Stems with subsidence had bone loss around the entire stem while stable stems had mainly proximal bone loss.

There are variations in bone loss with the size of the stem. Large stems increase bone loss (104, 105). However, there are published studies showing

bone loss in the femur after tibia osteotomy (106), indicating there might be a posttraumatic bone loss in the entire leg. The main reason for bone loss is thought to be partial weight bearing and stress shielding. Boden compared BMD in 20 patients randomized to partial or full weight bearing. The group with partial weight bearing had lost significantly more bone in Gruen zones 1, 4 and 5 after 3 months, compared to those with full weight bearing (87).
The clinical consequences of stress shielding and bone remodelling are still not fully understood. But there is no doubt that bone loss will make future revisions more complicated.
There are several medications for treating low BMD. We must note that this treatment may influence both stability and bone remodelling after implant operations. There are studies reporting prevention of prosthetic migration after treatment with clodronate (107) and reduction of bone resorption after treatment with risedronat (108) and alendronat (109). On the other hand, there are also published studies where alendronat did not influence stability (110). In future DXA studies medication treating low BMD should be registered. Perhaps we should treat our patients with medication against bone loss before operating? Prieto-Alhambra et al. did a retrospective analysis of all patients undergoing primary total arthroplasty of the knee (n=18 726) and hip (n=23 269) in 1986-2006 in the United Kingdom's General Practice Research Database. Among patients undergoing lower limb arthroplasty, bisphosphonate use was associated with an almost twofold increase in implant survival time (111).
A DXA scan is typically used to diagnose and monitor osteoporosis. But as bone loss has also been recognized as a problem around implants the

method has been applied to peri-implant bone remodelling. Previously, orthopaedic surgeons recognized bone loss on conventional x-rays, but had no possibility to measure it precisely. DXA has high precision with a coefficient of variation (CV) of less than 5 % in prospective studies (94, 112, 113). This creates the opportunity to differentiate between different implants. It has not been possible to distinguish between bone cement and real bone using DXA. The BMD has been measured with higher absolute values around cemented implants compared to uncemented. Manual exclusion of cement decreased the precision (CV) from 1.6% to 3.6% (p=0.001) in Wilkinson's study of periprosthetic BMD changes (94). When comparing bone loss between implants the cement might be excluded by reducing the absolute value by 20% (94).

1.8 Radiostereometric analysis (RSA)

RSA is a radiographic method enabling highly accurate evaluation of three-dimensional movements (114). Its main use has been assessment of joint replacement. The technique used in **paper 2** is based on the principles described by Selvik (115). The method calculates three-dimensional movement of rigid bodies in relation to each other. In orthopaedic studies spherical tantalum markers implanted into the bone and fixed to the prosthesis often define the rigid bodies. In addition geometric markers, such as the femoral head, are used.

RSA measurements of implant migration the two first years after surgery have proved to be highly predictive for later clinical failure (33, 116-119). The high precision of the method limits the number of patients exposed to new designs

until they are proven. Clinical fixation failure and loosening of cemented and cementless stems followed by radiostereometric analysis (RSA) have been associated with increased subsidence and rotation into retroversion (120-122). The method is well accepted and should be mandatory as part of the clinical documentation of new implants(114).

2. AIM OF THE THESIS

The aim of this thesis was to investigate if a new, thin hydroxyapatite coating (Bonemaster®) could give benefits to implant surgery when it comes to bone remodelling and migration. This was the first human implantation of Bonemaster®, and we designed the study as a safety study.

Paper 1 aimed to evaluate DXA as a method to measure bone mineral density in implant research.

Paper 2 aimed to compare Bonemaster® to a well-documented coating (HA) by clinical scoring and the use of DXA and RSA on a femoral stem.

Paper 3. Based on the results from **paper 2** we wanted to determine if the new coating, Bonemaster®, could induce formation of bone when implanted in muscles as a coating on titanium implants.

3.PATIENTS AND METHODS

3.1 Patients

Paper 1.

A methodological clinical study.

23 patients (15 women) were recruited from Diakonhjemmet hospital (20 patients) and Ullevål University Hospital from September 2007 to June 2008. Mean age at time of operation was 64 (34-82) years. Inclusion criteria were indication for THA with uncemented stem. Exclusion criteria were infection, revision arthroplasty, marked bone loss or severe morbidity. All patients were operated with a Corail (DePuy International Ltd.), uncemented HA coated stem and either Kronos cemented cup in Diakonhjemmet Hospital or Ogee (DePuy) cemented cup at Ullevål University Hospital. Measurement of bone mineral density was performed postoperatively after 1, 5 and 14 days and after 3 and 12 months. Two patients did not meet for the 14 days measurement, one patient did not meet for the 3 months measurement, and five patients did not meet for the 12 months measurement.

Paper 2.

A prospective randomized clinical study.

55 hips with osteoarthritis (OA) (50 patients, 31 women) were recruited from Diakonhjemmet hospital (30 hips) and Ullevål University hospital (25 hips) between December 2003 and June 2005. Mean age at the time of operation

was 63 (27–81) years. The patients were randomized to treatment with Taperloc (Biomet), an uncemented stem, coated with either plasma sprayed HA or Bonemaster®. All patients received a 28 mm cobalt-chromium head and a cemented cup, SHP (Biomet). Patients under 80 years with end stage osteoarthritis were included. Exclusion criteria were infection, revision arthroplasty, marked bone loss or severe morbidity. The patients were followed at 3, 6, 12 and 24 months postoperatively. One patient was lost to follow up because of a periprosthetic fracture 6 weeks after inclusion.

Paper 3.

An experimental animal study.

12 grey female Chinchilla rabbits were used in this animal study. They were 16 weeks old and 2.9-3.4 kilos on arrival.

Implants with 4 different surfaces were operated into each animal's spine muscles: (A) Grit blasted and Bonemaster® (GB-BM), (B) Porous titanium coating (PC), (C) Porous titanium coating and Bonemaster® (PC-BM), and (D) Porous coating and hydroxyapatite (PC-HA).

3.2 DXA (dual energy x-ray absorptiometry)

Dual energy X-ray absorptiometry (DXA, previously DEXA) is a method for measuring BMD. DXA is based on the method of X-ray spectrophotometry developed in the 1970s (123). It was introduced commercially as the direct successor to dual photon absorptiometry (DPA) in 1987. The fundamental physical principle behind DXA is the measurement of the transmission of X-

rays with high and low photon energies. The main advantages of an X-ray system over a DPA radionuclide system are shortened examination time due to an increased photon fluency of the X-ray tube, greater accuracy and precision resulting from higher resolution, and removal of errors due to source decay (124). The preferred anatomic sites for DXA measurement of bone mineral include the lumbar spine and the proximal femur. Developments in software analysis technique have made it possible to use it adjacent to metal implants.

Two X-ray beams with different energy levels are aimed at the patient. When soft tissue absorption is subtracted, the BMD can be determined from the difference in attenuation of the two x-ray beams. In their original description of the DXA technique in 1985, Ruth et al. suggested two methods of generating the dual energy x-ray spectrum (125), either K-edge filters or kVp switching. A K-absorption edge filter splits the polyenergetic x-ray beam into high- and low-energy components. kVp switching involves switching the high voltage generator between high and low kVp during alternate half cycles of the mains supply. First generation DXA scanners used a pencil beam coupled to a single detector in the scanning arm. A significant development in DXA technology has been the introduction of a fan beam. Fan beam studies are acquired by the scanning arm performing a single sweep across the patient instead of the two-dimensional raster scan required by pencil beam geometry. As a result scan times have been shortened from around 5 to 10 minutes for the early pencil beam scanners, to 10 to 30 seconds for the latest fan beam systems. Another advantage of fan beam systems is higher image resolution.

To analyze a DXA scan the raw data is processed to create a pixel-by-pixel map of BMD over the entire scan field. An edge detection algorithm is used to find the bone edges. The total projected area of bone is then derived by summing the pixels within the bone edges and the reported value of BMD calculated as the mean BMD over all the pixels identified as bone (125). Dual energy X-ray absorptiometry is the most widely used and most thoroughly studied bone density measurement technology. Studies of radiation dose to patients from DXA scans confirm that it is small compared to many other methods involving ionizing radiation. Patient dose in DXA procedures is less than the daily dose from natural background radiation (126).

DXA measurements after THA are usually reported as change in BMD in different regions of interest (ROI) around the implant (89, 103, 127). Software from the manufacturer often includes an orthopaedic version with standard analyses of the Gruen zones around a stem in proximal femur (f.ex. Progedy: Lunar, Madison, WI).

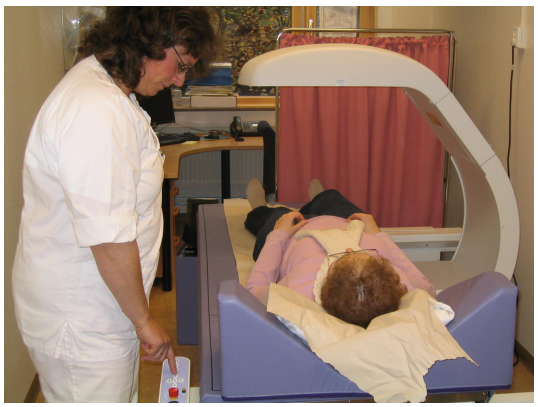

Figure 3. The DXA machine at Diakonhjemmet Hospital.

Figure 4. The author analyzing DXA results.

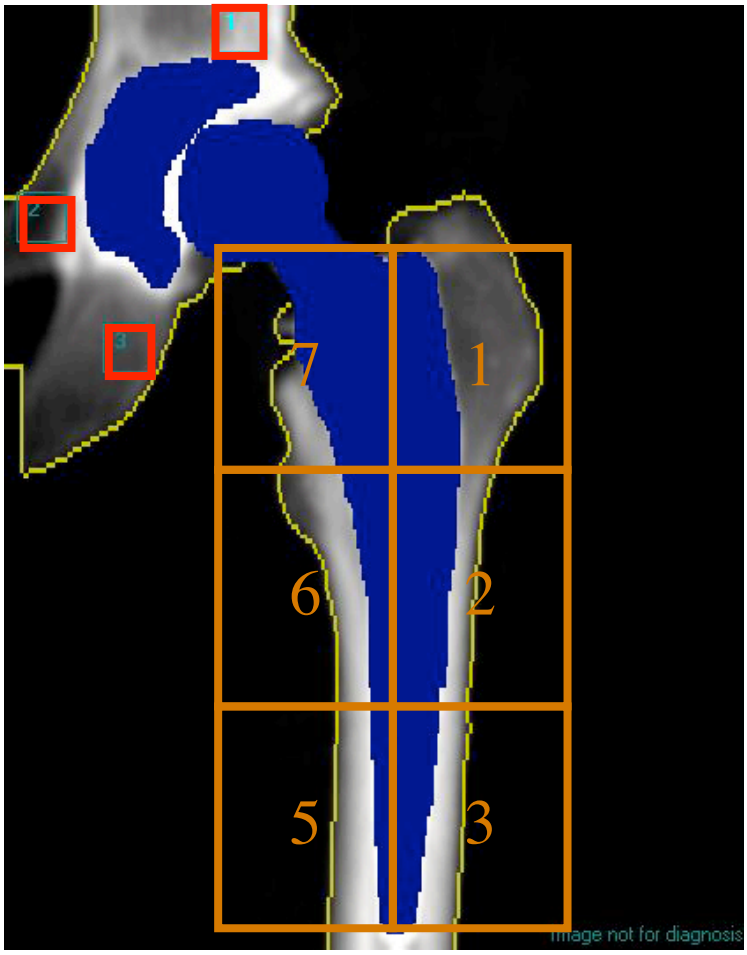

Figure 5. Regions of interest in DXA.

3.3 RSA (Radiostereometric analyses)

RSA in **paper 2** depends on spherical tantalum markers implanted into the bone or fixed to the prosthesis. The object to be studied is radiographed with a calibration cage, usually placed underneath the patient, in the picture. The calibration cage contains tantalum markers in predetermined positions, defining a coordinate system. Two x-ray tubes angulated about 40 degrees to each other are used to project simultaneous exposures of the patient's markers (*Figure 6*). The patient's markers and the implant are thus projected into a predetermined coordinate system. By repeating examinations at different time intervals, three-dimensional movement of the implant over time can be determined.

The accuracy of the measurements depends on the number of markers, how well dispersed they are in the different planes, the quality of the radiographs, and the calibration cage. Manual measurements have been replaced by digital measurements and software has been developed that automatically localizes and measures the markers from the calibration cage and the femoral head. One standard deviation can be as low as 10 microns for migration and 0.05 degrees for rotation.

In clinical studies it is recommended to perform double examinations to calculate precision error. Two sets of radiographs are taken with reposition of the patient between the scans. Precision is commonly expressed as the absolute mean value of all the recorded differences between double examinations with a standard deviation of 1.96 (114, 128). Valstar has published a document suggesting standardization of RSA investigation to facilitate comparison of outcomes reported by different research groups (129).

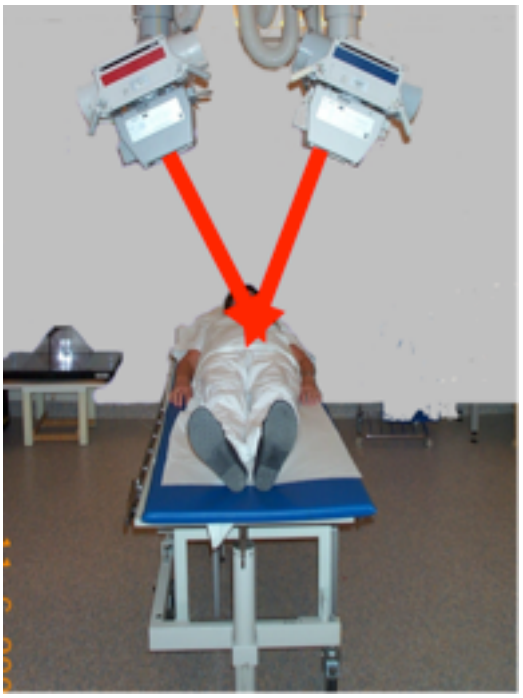

Figure 6. The 2 x-rays in RSA are taken simultaneously, angulated 40 degrees to each other.

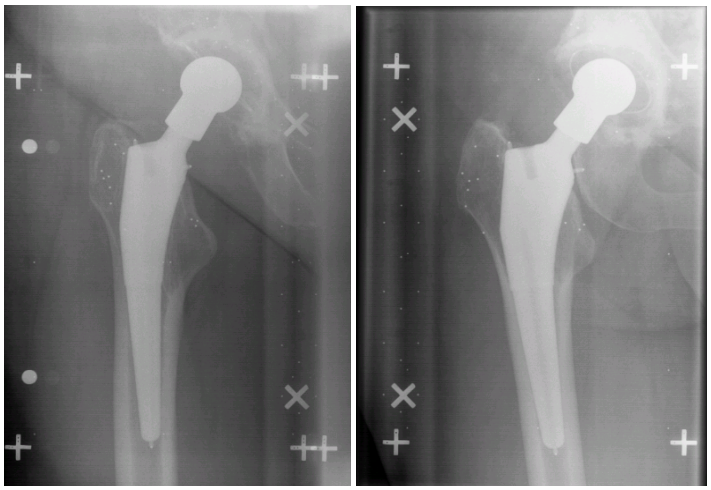

Figure 7. A pair of RSA-pictures where the cage markers are visible.

Figure 8. Radiographer Stine Gundersen checking x-ray quality.

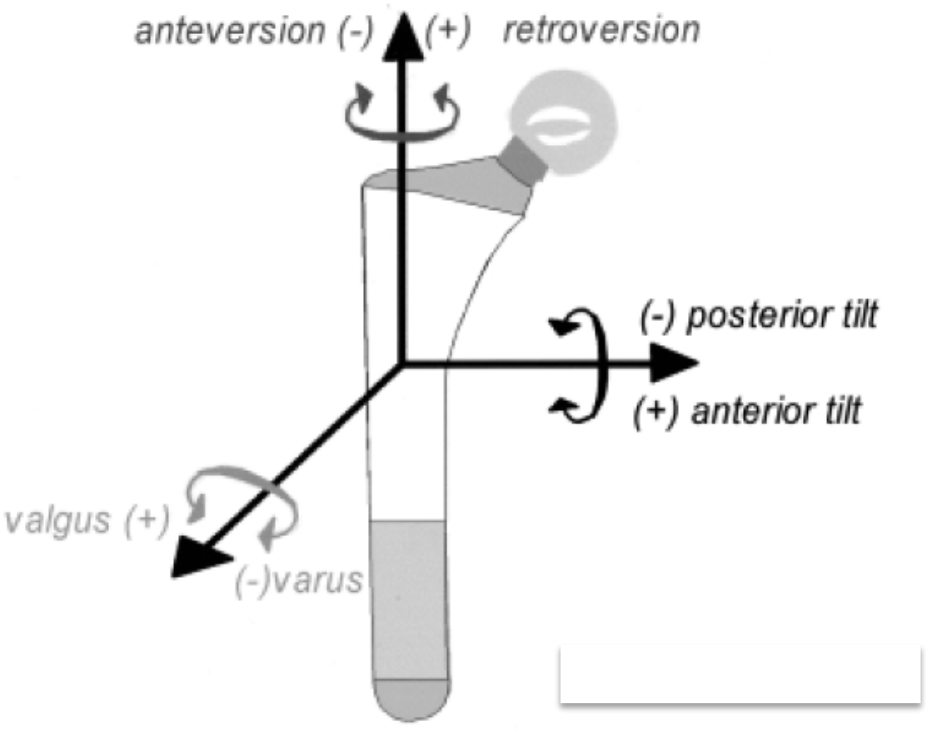

Figure 9. The coordinate axes used in RSA.

3.4 Radiography

Conventional radiographs with AP (*Figure 10*) and lateral views are the standard method for follow up of hip prostheses (130). With this method the implant needs to move by least 5 mm between two examinations to be detected by visual analysis (131).

Separation of the proximal femur in 7 zones (Gruen zones) in anterior-posterior and lateral view have become generally accepted (132). Around the cup DeLee and Charnley (133) divided the interface into three areas where the middle sector had 90 degrees. In our study we divided the acetabulum in three equal areas of 60 degrees. Measurements of varus-valgus of the stem or positioning of the cup are often performed, but may be criticized because of poor precision and variations in definitions. Other variables possible to register on conventional radiographs are resorption of calcar, heterotopic bone formation, trabecular remodelling, cyst formation and pedestal formation. Evaluation of radiolucent lines and migration is of crucial importance. Small dark lines between the implant and the bone may represent bone resorption and be prognostic for mechanical loosening. The extent of these lines is defined using the aforementioned zones. Migration of implants is better measured by radiostereometric analyses than conventional radiographs. Although there are methods (Martell) where the radiographs are digitally measured which are more suitable for larger patient groups (134), radiostereometric analyses are more precise and less sensitive to positioning of the patient.

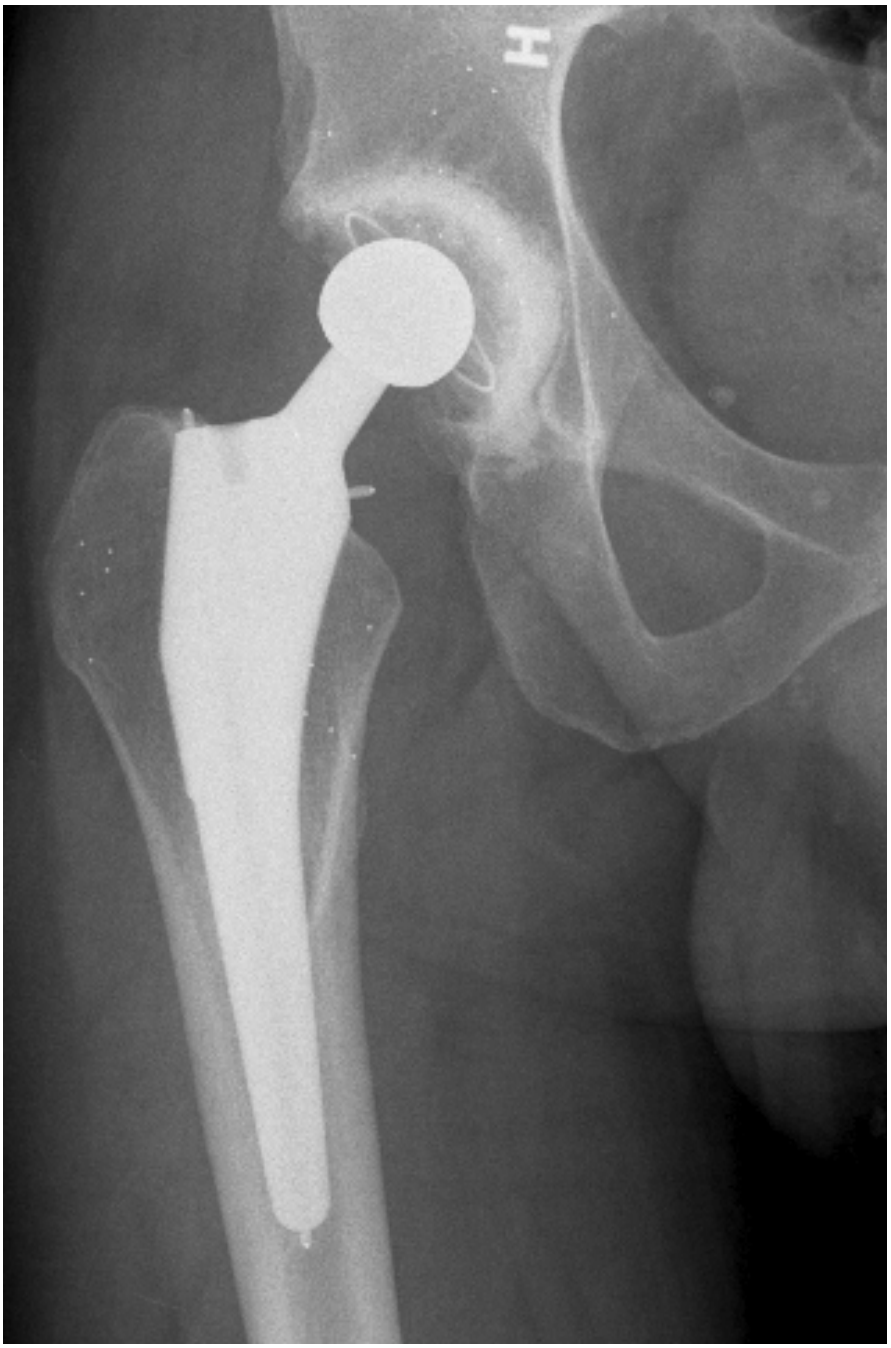

Figure 10. Ordinary x-ray with tantalum markers in proximal femur.

3.5 Clinical evaluation

Harris Hip Score was introduced in 1969 and has since been widely used to clinically evaluate hip function. It consists of a rating scale with a maximum of 100 points. The score includes pain, function, activities of daily living, motion

and deformity. It has a high reliability and validity (135). In HHS the orthopaedic surgeon answers all the questions and does all the examinations. Oxford Hip Score is a12 point patient-based questionnaire developed and validated specifically to assess function and pain after THA (136).
In addition we recorded leg discrepancy and range of movement.

3.6 Histology

The implants in the animal study were dissected with surrounding tissue and immediately fixed in 4% buffered formaldehyde. The fixed samples were dehydrated in a series of alcohol solutions and embedded in methyl methacrylate (MMA). Each sample was cut into several sections and grinded to a thickness of 10-20 microns to optimize staining. The important issue was how to differentiate bone from soft tissue and from HA coating. We first analyzed one series stained with methylene blue and basic fuchsine, and then another stained with Massons-Goldners. It was difficult to decide what was bone with methylene blue and basic fuchsine. Massons-Goldners stains bone green and makes it possible to distinguish bone from other tissue. HA coating also stains green, but the coating had another structure and was therefore distinguishable.

3.7 Statistics

The statistical analysis of BMD and RSA results to compare Bonemaster® to HA was done using non-inferiority testing (SPSS for Mac, SPSS Inc. Chicago, Illinois, USA Version PASW 18.0). The DXA results were calculated as

change in percent. RSA results were presented as signed values with SEM and 95% Confidence Interval. The DXA and RSA results were not normally distributed. The 2 groups were compared with Mann-Whitney U. In **paper 1 and 2** the changes from post operative DXA to later follow up were analyzed with Wilcoxon Signed Rank Test.

A power analysis was performed after the study in **paper 2** started. Based on an estimated clinically important difference in BMD of 10% (SD 10%), stem migration of 0.6 mm (SD 0.6 mm) and stem rotation of 0.7 degrees (SD 0.7 degrees) between groups, the sample size calculation indicates 17 patients were required in each group to achieve 80% power at a 0.05 significance level. Due to the risk of patient dropout, at least 24 patients were included in each group.

To calculate precision error, DXA examinations were repeated the same day with reposition between the scans. The differences between these paired BMD were used to calculate the coefficient of variation (CV) for each ROI. $CV\% = 100 \times [(\delta/\sqrt{2})/\mu]$ for each ROI, where δ represents the standard deviation of the difference between the paired BMD measurements, and μ is the overall mean of all the BMD measurements for each individual ROI.

In **paper 3** we had 48 samples, 12 of each coating, and the result was categorical. In this material we compared groups with Fisher's exact test for 2 x 4 table in STATA® (statistical program).

4.SUMMARY OF RESULTS

Paper 1

We found no change in BMD during the first 2 weeks after operation with total hip arthroplasty (*Figure 11*). Between 14 days and 3 months there was a mean bone loss of 8%, ranging from 18% in Zone 7, to 4% in Zones 4 and 5 ($p<0.05$ for all zones). There was restoration of bone in all zones from 3 to 12 months follow up. This restoration was from 2-8% and statistically significant in zones 2-6. The BMD decreased most in zone 7, by 18% after 3 months. The precision (CV) of DXA measurements varied from 0.8% in Gruen zone 4, to 5.1% in zone 7. Mean CV was 1.8%.

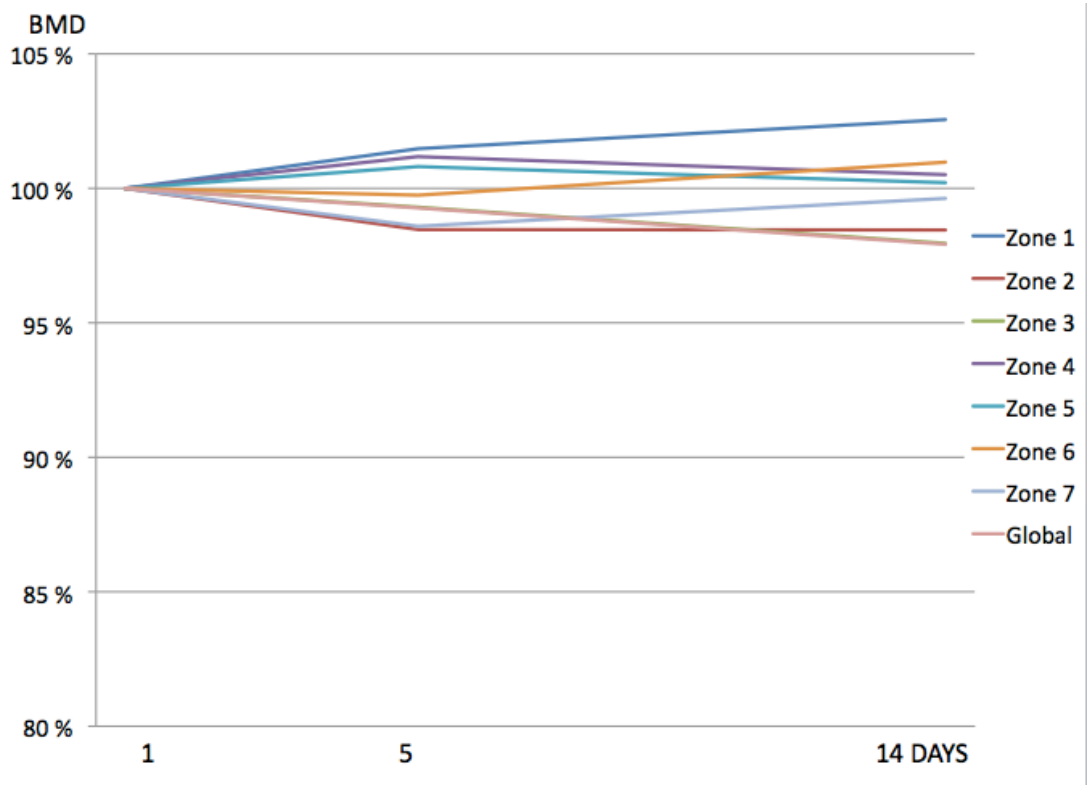

Figure11. BMD in ***paper 1.***

Changes in bone mineral density (BMD) in different regions, the first 14 days after operation with an uncemented femoral stem. Results are medians as a percentage of the first postoperative value.

Paper 2.

DXA. We included 55 patients and randomized between the two different hydroxyapatite coatings. We found that uncemented stems coated with Bonemaster® resulted in higher bone mineral density than plasma sprayed HA coating in the area of the femur with most trabecular bone (Gruen zone 1). In all other Gruen zones there was no significant difference between the two groups (*Table 1*).

RSA. The mean subsidence (CI) of the stem centre was 0.28 (± 0.18) mm for Bonemaster® and 0.25 (±0.32) mm for HA (*Figure 12*). Precision for subsidence was 0.11 mm. Both groups had retroversion lower than the precision in this direction (0.66°). The migration pattern for both stems showed that they moved during the 3 first months after surgery, and then stabilized.

With non-inferiority testing there were no significant differences between groups in any migration or rotation after 2 years.

Clinical results. Harris Hip score increased from 55 (pain score 20) pre operatively to 95 (41) after 2 years in the Bonemaster® group, similar to the increase from 52 (18) to 89 (38) in the HA group. Oxford Hip Score improved from 39 preoperatively to 16 after 2 years in the Bonemaster® group and from 35 to 19 in the HA group. The differences after 2 years were not statistically significant**.**

There were no radiolucent lines around the stems after 2 years.

*Table1: BMD in **paper 2**.*

Periprosthetic changes in bone mineral density around hydroxyapatite- (HA-) and Bonemaster-coated Taperloc stems measured by dual energy x-ray (DXA). Results are given in percentages (standard deviation) of postoperative values after 3 months, 6 months, 1 year and 2 years.

Gruen zone	n	3 months	n	6 months	n	1 year	n	2 year
1 Bonemaster	30	92 (19)	29	94 (25)	31	90 (26)	30	87 (19)
HA	20	83 (14)	22	79 (13)	22	76 (15)	22	79 (18)
2 Bonemaster	30	89 (10)	29	92 (8)	31	90 (10)	30	87 (14)
HA	20	90 (10)	22	90 (8)	22	89 (9)	22	86 (10)
3 Bonemaster	30	93 (7)	29	96 (6)	31	94 (8)	30	90 (12)
HA	20	94 (5)	22	96 (5)	22	95 (7)	22	92 (9)
4 Bonemaster	30	95 (5)	29	95 (6)	31	94 (5)	30	90 (9)
HA	20	96 (5)	22	95 (4)	22	94 (6)	22	90 (7)
5 Bonemaster	30	94 (7)	29	97 (7)	31	96 (9)	30	90 (11)
HA	20	97 (5)	22	97 (6)	22	93 (10)	22	88 (12)
6 Bonemaster	30	93 (9)	29	94 (8)	31	94 (9)	30	89 (11)
HA	20	94 (7)	22	86 (23)	22	90 (10)	22	88 (9)
7 Bonemaster	30	82 (13)	29	77 (14)	31	73 (15)	30	70 (16)
HA	20	83 (9)	22	77 (11)	22	73 (12)	22	69 (13)

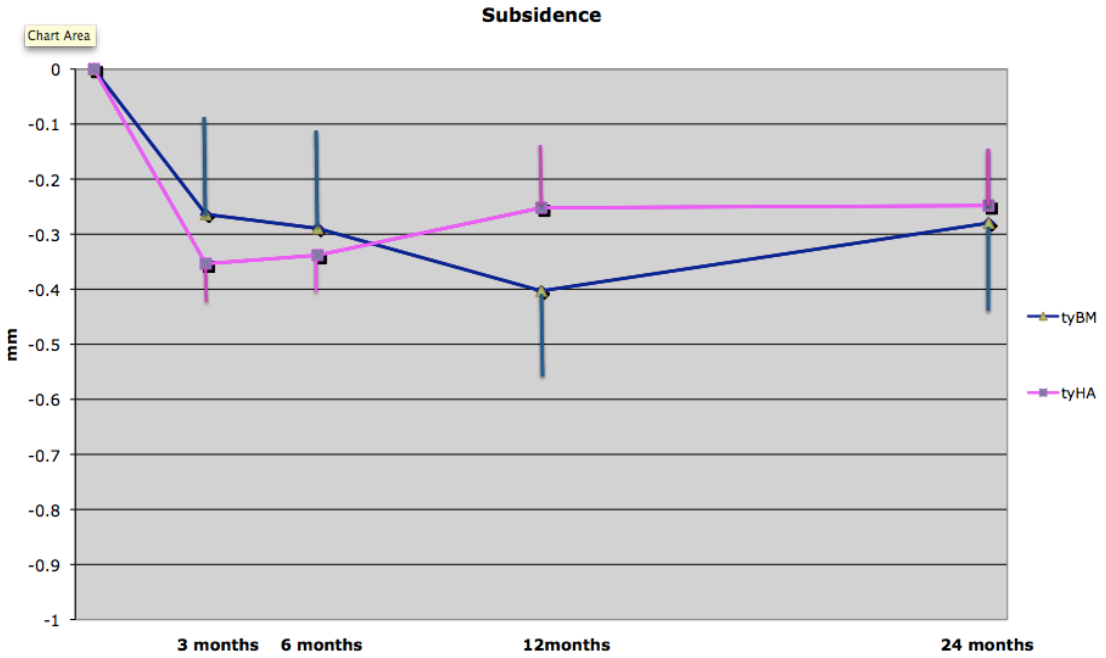

*Figure 12. Subsidence in **paper 2**.*

Subsidence of 0.25 (hydroxyapatite/HA) and 0.28 (Bonemaster® /BM) millimetres the first 2 years after implantation of HA- and BM-coated Taperloc stems analyzed by radiostereometric analysis (RSA). Results in millimetres with standard error of mean after 3 months, 6 months, 1 year and 2 years. (tyBM/tyHA = translation in y-direction for BM and HA).

Paper 3

In this animal study set up to investigate bone induction we found new bone in muscle (*Figure 13*). There was no obvious difference in amount or maturity of bone tissue from 6 to 12 weeks.

The grit blasted implants coated with Bonemaster induced bone in 4 of 11 cases. Implants treated with only titanium porous coating induced bone in 5 of 12 cases, while only 1 of 12 implants with both Bonemaster and porous coating induced bone. Around implants with plasma sprayed HA we found no bone.

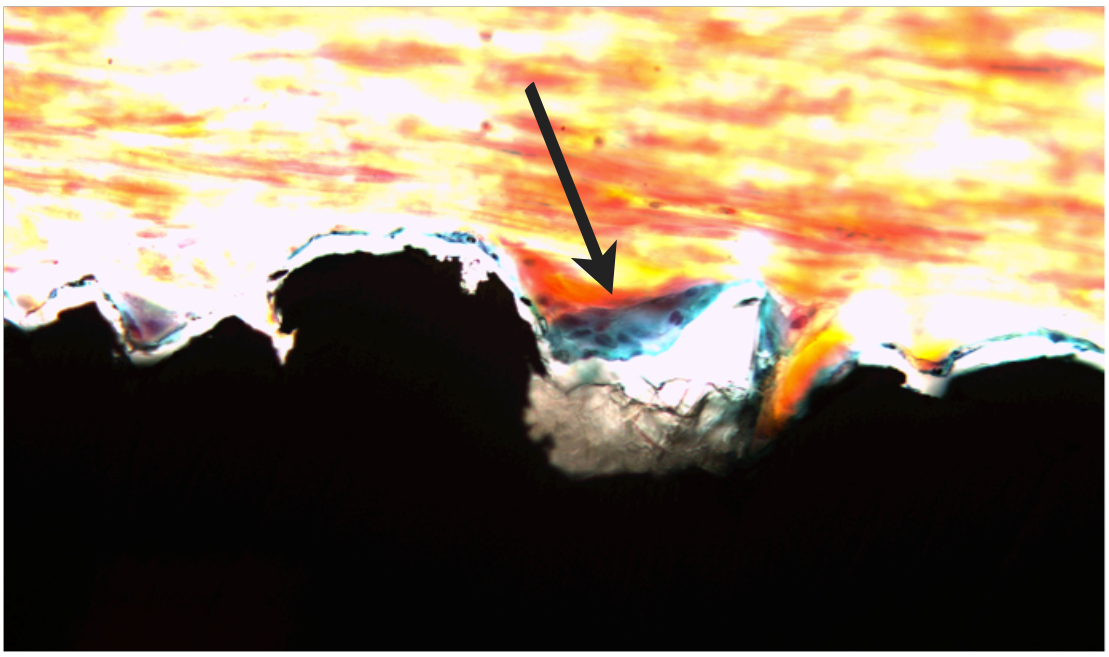

*Figure 13. Osteoinduction in **paper 3**.*

Light micrograph (primary magnification 40x) of bone formation seen as a thin green line along the implant surface (arrows). The implant is grit blasted with Bonemaster®.

5. GENERAL DISCUSSION

Uncemented titanium stems have demonstrated satisfactory long-term survival rates at 10-20 years follow up (11, 43, 137, 138). One major concern with regard to long-term stem performance is progressive periprosthetic bone loss that may reduce implant stability, leading to subsidence and aseptic loosening (139). Stress mediated bone resorption at the metaphyseal region of the proximal femur as a result of distal load transfer may affect the clinical outcome of a total hip arthroplasty and will make revision surgery difficult (140). There is also an increased risk of periprosthetic fractures in cases of substantial bone loss around an implant. The consequences of bone loss for

implant survival are still discussed, however, it seems reasonable to preserve the bone and that monitoring changes in BMD is advantageous to differentiate among implants. In this scenario it was encouraging to find higher BMD with a new coating in **paper 2**. The difference between Bonemaster® and HA was significant in Gruen zone 1, where it is mostly trabecular bone. The difference was probably found here due to the higher bone turnover in trabecular bone. In the animal study we also found results in favour of the new coating compared to traditional HA. We found new bone tissue in muscle in all groups except for those with plasma sprayed HA. In **paper 1** we found that BMD increased from 3 to 12 months. Perhaps the phenomenon of stress shielding is less prominent than earlier suggested? The difference in **paper 2** was probably not due to differences in loading as the stems moved equally, as measured by RSA. Other factors than changes in mechanical loading may be the reason for the post-traumatic bone loss found after arthroplasty. Unfortunately, the study in **paper 2** was initiated without a proper power analysis. In the protocol we planned to include 100 patients, however, after a proper power analysis we ended the inclusion after 55 hips to reduce the inclusion time. At that time we had randomized 31 hips to Bonemaster and 24 hips to HA. It would have been correct to do the power analysis ahead of the first randomization to decide number of patients to be included. We also included both hips of five patients. From a statistical perspective we should only include one hip from each patient. In **paper 1 and 2** the femoral component was examined separately from the acetabular component, however, this approach can always be disputed. One issue to raise is that when combining stems and cups that have performed well separately, there is

a risk that their use in combination will behave differently. In both studies we used reversed hybrid, meaning uncemented stem combined with cemented cup, because this is a theoretically promising combination. Both uncemented stems and cemented cups have performed well (39, 43, 47, 141).

Paper 3 was initiated by the results of **paper 2**. In the clinical study we found that Bonemaster® protected against bone loss in trabecular bone compared to HA. However, in the animal study, porous coated titanium turned out to be osteoinductive as well as the Bonemaster® coated implants. No new bone was seen around plasma sprayed HA coated implants. Given this we should have included a control group with porous titanium in the clinical study. The results could indicate that physical properties are more important than chemical ones. The irregular surface of the underlying porous titanium is better preserved by a thin coating like Bonemaster®, than with HA. We found very limited amounts of bone. In further research we would like to include immunohistochemistry, electron microscopy or PCR in addition to light microscopy to increase our ability to detect bone. However, these methods might be challenging when studying a metal surface.

HA has previously been shown to be osteoinductive when implanted as granulas sub cutaneous in dogs (142). We performed implantation where HA was coated on titanium discs because that is the relevant setting in orthopaedic implant surgery. A difference in bone formation between species has been shown in that larger animals seem to produce bone where smaller animals do not (143). Perhaps HA on titanium surface could induce bone in larger animals and people, even though we did not find it in rabbits.

Bone remodelling

Prospective studies of cementless femoral stems have shown significant bone loss (10-40%) in the calcar region after 1-4 years (37, 86, 93, 101, 144-146). This was also the result in **papers 1 and 2**. A weakness in **paper 2** arose because one of the hospitals bought a new DXA machine during the study. We had to calculate a transformation formula based on examinations done on both machines (old and new) the same day. The calculation was based on examinations of five patients from our study. In both **paper 1** and **paper 2** we did double examinations of the patients on the same day for almost every examination. The purpose was to calculate coefficient of variation (CV) to estimate the quality of our measurements. In longitudinal studies BMD changes are dependent on reproducibility. It is therefore important to have estimated the precision of the measurements.

Some studies following patients for up to 10 years have shown progressive recovery or minimal loss of BMD after the first to second postoperative year (88, 93, 101, 147). In **paper 1** we found restoration of bone in all Gruen zones from 3 to 12 months. However, in paper 2 there was continuous bone loss the first 2 years. Cementless stems with reduced stiffness were introduced to facilitate proximal load transfer and thereby reduce proximal bone loss. To evaluate the early performance of a less stiff stem, Kärrholm et al. compared Epoch with the stiffer stem Anatomic (86). At two years postoperatively, the Epoch stems had fewer sclerotic lines surrounding the stem and achieved

excellent primary fixation. Despite this rigid fixation, the proximal loss of bone-mineral density was less than that associated with the stem with a stiffer design. Karachalios et al. (147) performed a prospective randomized study on four different stem designs and reported a slow progressive recovery of initial bone loss up to 10 years postoperatively in all groups, postulating that the phenomenon of stress-shielding is overestimated in the literature. Merle et al. (148) have investigated the bone remodelling pattern around an uncemented stem from 10 to 17 years after surgery. They found no clinically relevant bone loss in this period. It seems that any bone loss in this period might be related to age and gender. We did not perform pre-operative measurements or measurements of the contralateral hip in any of our studies. Several authors have stated there is a correlation between BMD before the operation and loss of bone after the operation; lower BMD leads to greater bone loss (92, 99, 149). Kiratli et al. did not find any correlation between preoperative values and postoperative bone loss (88). The importance of early bone loss around proximal femur stems is still unclear.

Limiting early bone loss seems reasonable to enhance early bone ingrowth and implant fixation. Plasma sprayed calcium phosphate coatings have been applied in different qualities and with various coating thicknesses, ranging from 40 microns (150) to 150 microns (151), and in other publications up to 300 microns (53, 152). Thinner plasma sprayed HA coatings have been recommended, because they give a strong fixation and reduce the risk of coating fracture (19, 153). In **paper 2** the plasma sprayed HA was approximately 60 microns thick. The new electrochemically deposited HA is

as thin as approximately 5 microns which ensures an even distribution and quick resorption (154). A thinner coating also minimizes the potential for particle shedding during insertion. Fewer particles in the joint mean less third body wear and less periprosthetic osteolysis (155-158). Thinner coatings also lower the risk of HA delaminating and preserve the porosity of the underlying metallic coating of the implant. An irregular implant surface increases the surface area, providing a larger contact and ingrowth area (159). EDHA, like Bonemaster, forms a needle-like porous structure (160) and enhances early stage fixation between implant and bone (161).

Addition of HA coatings, both plasma sprayed and electrochemically deposited, has led to increased mechanical fixation and bone ingrowth compared to an uncoated titanium control after 4 weeks in dog models (154). We await the long-term results of implants with these new EDHA coatings.

Radiostereometric analysis

RSA is an accurate and precise method for evaluating motion of implants *in vivo*. The association between initial micro instability and later aseptic loosening of implants is well documented (33, 117, 118, 120) and make RSA a valuable tool in clinical studies with new implants and technologies. HA coating is thought to increase the initial stability of implants because of early bone ingrowth (78, 162). Because of the high precision and accuracy fewer patients and shorter follow-up time is needed in RCTs. We also need to consider the design of the stem when evaluating migration pattern. In **paper 2** the stem subsided the three first months post operatively and then stabilized.

This migration pattern has also been shown with other HA coated implants. Thien et al. (163) published the same pattern of subsidence for 43 ABG stems. However, both HA-coated cementless stems in Kärrholm's paper comparing Epoch to Anatomic had migration close to zero after two years (86). For the clinically proven Corail stem, Campbell et al. (164) documented more subsidence (0.58mm) than we found for Taperloc in the first 2 years. Corail, however, had the same migration pattern with stability after 6 months. As both Corail and Taperloc have good clinical long-term results (80), it appears that subsidence during the first months, which stabilises within a year is typical for these designs of HA coated uncemented implants.

RSA is time consuming, expensive and demands personnel trained in the procedure. Therefore it cannot be routinely used. Recently the method has been further developed with markerless RSA (165). Although this makes the procedure easier, it remains to be used as a tool in research.

6. CONCLUSIONS

Paper 1

We found similar BMD values during 3 different measurements in the first 14 days after implantation of an uncemented femoral stem. Baseline measurement for bone remodelling studies with DXA can therefore be done at any time in this interval.

Paper 2

We found higher bone mineral density in Gruen zone 1 in the Bonemaster® group compared to plasma sprayed HA.

We found no differences between Bonemaster® and HA in migration.

We found no differences in clinical results between the two groups.

Taperloc stem with Bonemaster® appears to be non-inferior to Taperloc stem with plasma sprayed HA concerning clinical and radiological results, bone remodelling and micromotion up to 2 years.

Paper 3

We found new bone tissue around titanium implants coated with Bonemaster® in rabbit muscles. Bonemaster® appears to be osteoinductive on a titanium surface.

7. SUGGESTIONS FOR FURTHER RESEARCH

The patients in **paper 1** will be followed further to get long term information about Taperloc with Bonemaster®. We have already had 5 years follow up and are looking forward to analysing and publishing this data. 10 years follow up is planned. Earlier literature on total hip arthroplasty suggests that minor changes to a specific implant may alter the result dramatically.

The osteogenesis around implants is not fully understood and we have to keep working with experimental studies to find the most advantageous surface. In similar animal studies there would be advantages in doing gene

expression analyses for bone markers like bone sialoprotein (BSP). These would be quality assurance and an opportunity to quantify the amount of bone.

NORSK SAMMENDRAG

Protesekirurgi i hofteleddet er av de mest kostnads-effektive behandlinger med tanke på økning i pasientens livskvalitet. Siden moderne protesekirurgis start i 1960 (Charnleyprotesen) har antall primærproteseoperasjoner I Norge økt gradvis til et nivå på omlag 5500 pr år på 1990-tallet og 6-7000 pr år etter år 2000. Det er i tillegg gjort omlag 1000 reoperasjoner per år. Dette gir en revisjonsrate på 15%. Ved revisjoner er hovedproblemet ofte ben tap (osteolyse) rundt implantatet.

Resultatene av sementerte og usementerte proteser fortsetter å være et diskusjonstema blant ortopeder. I data fra det norske leddregisteret ser det ut til at usementerte kopper har en dårligere 10 års overlevelse enn sementerte, mens noen usementerte stammer har en like god overlevelse som de sementerte. En av de usementerte stammene som har god overlevelse I litteraturen er Taperloc. Denne er tidligere benyttet I Norge uten beinmineral belegg (hydroxylapatitt/HA).

Vi har i **paper 2** prøvd ut Taperloc protesen med to forskjellige HA belegg I en multisenterstudie med klinisk og billedmessig evaluering. Radiostereometri (RSA) er en svært presis metode til å vurdere om protesen beveger seg. Dual x-ray absorptiometry (DXA) er en presis måte å måle bentetthet på. Studien ble gjort for å sammenligne de to beleggene og for å kontrollere om det nye

Bonemaster® var like bra som det tradisjonelle HA. Vi fant ut at pasientene som fikk proteser med det nye belegget hadde litt høyere bentetthet rundt øvre del av stammen de to første årene etter operasjon. Det var ingen forskjell i hvor mye protesene beveget seg. Siden tap av ben er en av hovedårsakene til at hofteproteser løsner er dette et gunstig resultat, men det gjenstår å se om det får betydning for langtidsresultatene.

I **paper 1** har vi sett på DXA som metode. DXA er kjent for å være en presis målemetode for bentetthet med usikkerhet på under 5 %. Likevel presenteres data fra sammenlignbare pasient grupper med svært forskjellig endring i bentetthet rundt samme type protese. Vi har derfor stilt spørsmål om varierende resultater kan skyldes måten vi måler på. Endring i bentetthet etter operasjon med hofteproteser blir vanligvis presentert som en prosentvis endring over tid, der utgangspunktet er den første post operative målingen. Dersom det er et raskt bentap de første ukene etter operasjonen, vil denne første referansemålingen bli svært forskjellig om den tas første post operative dag eller etter to uker. Dette vil videre påvirke resultatene som presenteres som prosentvis endring fra første måling. Vi gjorde bentetthetsmålinger første, femte og 14. dag etter operasjon og fant ingen store forskjeller i denne perioden. Konklusjonen blir derfor at man kan utføre referansemålingen innenfor de to første ukene etter operasjonen.

På bakgrunn av at vi fant høyere bentetthet i gruppen som fikk protese med Bonemaster® i **paper 1** ønsket vi å undersøke denne overflatens evne til å stimulere ben dannelse. Dette gjorde vi i paper 3, en dyrestudie hvor fire små titanskiver med ulik overflate ble operert inn i rygg- og setemuskel hos kaniner. Overflaten med Bonemaster® viste seg å stimulere bløtvev til å produsere

nytt ben. Dette vil være et fremskritt i protesekirurgi, der vi ønsker å unngå bentap rundt implantatet.

APPENDIX

Appendix 1: HHS

Appendix 2: Oxford

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TAPERLOC HA STUDY
HARRIS HIP SCORE

00352

Patient Study Number: | | | |

PATIENT DETAILS:

Hospital No.: | | | | | | | | | | **Hospital:** | | | | | | | | | | |

Surgeon | | | | | | | | | | | **Date of Exam:** | | / | | | / | | | (d/m/y)

SIDE OPERATED:
Left ○
Right ○ Shade Circles Like This -> ●

FOLLOW-UP: ○ Pre Op ○ Immediate Post Op ○ 3 months ○ 6 months ○ 1 year ○ 2 year ○ 3 year ○ 5 year ○ Other Years: | | Months: | |

1) PAIN

○ None/Ignores
○ Slight, Occasional, No Compromise in Activity
○ Mild, No Effect on Ordinary Activity, Pain After Usual Activity, Uses Aspirin
○ Moderate, Tolerable, Makes Concessions, Occasional Codeine
○ Marked, Serious Limitations
○ Totally Disabled

2) FUNCTION: A) GAIT (Walking Maximum Distance)

i)LIMP	ii)SUPPORT		iii)DISTANCE WALKED
○ None	○ None	○ 2 Canes	○ Unlimited
○ Slight	○ Cane, Long Walks	○ 2 Crutches	○ 500m - 1 Km
○ Moderate	○ Cane, Full Time	○ Unable to Walk	○ 100m - 500m
○ Severe	○ Crutch		○ Indoors Only
○ Unable to Walk			○ Bed & Chair

B) ACTIVITIES

i)STAIRS	ii)SOCKS/TIE SHOES	iii)SITTING	iv)PUBLIC TRANSPORT
○ Normally	○ With Ease	○ Any Chair, 1 Hour	○ Able to Enter
○ Normally with Bannister	○ With Difficulty	○ High Chair, 1/2 Hour	○ Not Able to Use
○ Any Method	○ Unable	○ Unable to Sit 1/2 Hour Any Chair	
○ Not Able			

3) DEFORMITY ○ No ○ Yes

Requires All Four of the following:
1. Fixed ADD Less Than 10 degrees
2. Fixed IRE Less Than 10 degress
3. Leg Length Discrepancy Less Than 1 1/4"
4. PFC Less Than 30 degrees

4) RANGE OF MOTION Record 10 degrees of Fixed Adduction as "-10 degrees ABD, ADD to 10 degrees." Similarly, 10 degrees of Fixed EXT. Rotation as "-10 degrees Internal Rotation, External Rotation to 10 degrees." Similarly, 10 degrees of Fixed External Rotation with 10 degrees Further External Rotation as "-10 degrees Internal, External Rotation to 20 degrees."

A.Permanent Flexion: | | | ° **C. Abduction To:** | | ° **E. External Rotation in Extension To:** | | °

B.Flexion To: | | | ° **D. Adduction To:** | | ° **F. Internal Rotation in Extension To:** | | °

Trendelenburg: ○ Pos ○ Level ○ Neg **Compensation Involved:** ○ Yes ○ No

Leg Length Discrepancy: ○ R Short ○ L Short ○ Legs Equal

True:	○ 0	○ 1/4	○ 1/2	○ 3/4	○ 1	○ 1 1/4	○ 1 1/2
	○ 1 3/4	○ 2	○ 2 1/4	○ 2 1/2	○ 2 3/4	○ 3	○ over 3
Apparent:	○ 0	○ 1/4	○ 1/2	○ 3/4	○ 1	○ 1 1/4	○ 1 1/2
	○ 1 3/4	○ 2	○ 2 1/4	○ 2 1/2	○ 2 3/4	○ 3	○ over 3

Surgeon Signature _____ **DATE:** | | / | | / | | (d/m/y

TAPERLOC HA STUDY
OXFORD - EVALUERING AV HOFTEFUNKSJON

04262

Pasientens Studie nr : ☐☐☐

Sett merket ● i en rute for hvert spørsmål

Pasientens ID-nummer: ☐☐☐☐☐☐☐☐☐

Sykehus: ☐☐☐☐☐☐☐☐☐☐

Evalueringsdato: ☐☐ / ☐☐ / ☐☐ **(dd/mm/åå)**

○ **VENSTRE** ○ PRE-OP ○ 6 UKER ○ 3 MÅNEDER ○ 6 MÅNEDER ○ 1 ÅR ○ 3 ÅR

○ **HØYRE** ○ 5 ÅR ○ 10 ÅR ○ 15 ÅR ○ Annet Spesifiser: **ÅR:** ☐☐ **MÅNEDER:** ☐☐

I LØPET AV DE SISTE 4 UKENE

Q1 Hvordan vil du beskrive smertene du vanligvis hadde i hoften?

○ Ingen
○ Meget svake
○ Svake
○ Moderate
○ Alvorlige

Q2 Har du hatt problemer med å vaske deg og tørke deg (over hele kroppen) på grunn av hoften?

○ Ingen problemer i det hele tatt
○ Meget få problemer
○ Moderate problemer
○ Svært vanskelig
○ Umulig å gjennomføre

Q3 Har du hatt problemer med å komme deg inn og ut av bilen, eller bruke offentlige transportmidler på grunn av hoften?(alt etter hva du vanligvis bruker)

○ Ingen problemer i det hele tatt
○ Meget få problemer
○ Moderate problemer
○ Svært vanskelig
○ Umulig å gjennomføre

Q4 Har du vært i stand til å ta på deg sokker, strømper eller strømpebukser?

○ Ja, med letthet
○ Med litt besvær
○ Med moderat besvær
○ Med stort besvær
○ Nei, umulig

Q5 Kunne du gjøre innkjøp av dagligvarer på egen hånd?

○ Ja, med letthet
○ Med litt besvær
○ Med moderat besvær
○ Med stort besvær
○ Nei, umulig

Q6 Hvor lenge har du kunnet gå før smertene i hoften blir alvorlige? (med eller uten stokk/krykker)

○ Ingen smerter/ mer enn 30 minutter
○ 16 til 30 minutter
○ 5 til 15 minutter
○ Kun rundt om i huset
○ Ikke i det hele tatt - alvorlige smerter når jeg går

I LØPET AV DE SISTE 4 UKENE

Q7 Har du vært i stand til å gå opp trapper?

○ Ja, med letthet
○ Med litt besvær
○ Med moderat besvær
○ Med stort besvær
○ Nei, umulig

Q8 Etter å ha spist (etter å ha sittet ved et bord), hvor smertefullt har det vært å reise seg fra stolen på grunn av hoften?

○ Ikke smertefullt i det hele tatt
○ Litt smertefullt
○ Moderat smertefullt
○ Meget smertefullt
○ Uutholdelig

Q9 Har du haltet når du går på grunn av hoften?

○ Sjelden/aldri
○ Av og til, eller bare i begnnelsen
○ Ofte, ikke bare i begynnelsen
○ Nesten alltid
○ Alltid

Q10 Har du fått plutselig alvorlige smerter - 'jagende', 'stikkende' eller 'kramper'- fra den gjeldende hoften?

○ Ingen dager
○ Kun 1 eller 2 dager
○ Noen dager
○ De fleste dager
○ Hver dag

Q11 Hvor mye har smerter i hoften forstyrret ditt vanlige arbeid (inkludert husarbeid)?

○ Ikke i det hele tatt
○ Litt
○ Moderat
○ I stor grad
○ Fullstendig

Q12 Har du hatt problemer med smerter i hoften når du ligger i sengen om natten?

○ Ingen netter
○ Kun 1 eller 2 netter
○ Noen netter
○ De fleste netter
○ Hver natt

OG TIL SLUTT: BARE ETTER OPERASJONEN

Har du hatt noen flere operasjoner i denne hoften?: **Ja** ○ **Nei** ○

Hvis ja: Når og hvor?: ☐☐ / ☐☐ / ☐☐ **(dd/mm/åå)** **Sykehus** ☐☐☐☐☐☐☐☐☐☐

Ble hoften erstattet?: **Ja** ○ **Nei** ○

Signatur _____

DATO: ☐☐ / ☐☐ / ☐☐ **(dd/mm/åå)**

Mange Takk For Hjelpen

Measurement of early bone loss around an uncemented femoral stem

A methodological study with dual-energy X-ray absorptiometry in 16 patients

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Background and purpose **Dual-energy X-ray absorptiometry (DXA) is a precise method to study changes in bone mineral density (BMD), including the pattern of bone remodeling around an implant. Results from implant studies are usually presented as changes in BMD as a function of time. The baseline and reference value for such calculations is the first measurement after the operation. The baseline measurement has been performed at different time points in different studies. If there is rapid bone loss immediately after an operation, this will influence the reference value and hence the results. To evaluate DXA as a method, we studied the very early changes by doing 3 DXA measurements within the first 2 weeks after surgery.**

Patients and methods **We included 23 hips in 23 patients who were operated with an uncemented total hip prosthesis (THP). Each Gruen region was measured with DXA at 1, 5, and 14 days, and 3 and 12 months after the operation. 16 of the patients completed all 5 follow-ups.**

Results **There was no detectable change in BMD in the first 14 days after the operation. In all zones, the lowest BMD was measured after 3 months.**

Interpretation **We conclude that DXA measurements done within 14 days after the operation can be used as reference measurements for later follow-up studies.**

The bone remodeling around hip prostheses appears to vary a great deal with different fixation methods and stem designs (Kiratli et al. 1996, Boden et al. 2004, Rahmy et al. 2004, Grant et al. 2005). Even with the same implant, researchers have reported a variety of bone mineral density (BMD) changes. In implant research, BMD results are most often given in percentage change relative to the first postoperative measurement. The postoperative measurement is used as a reference to avoid measuring the changes in BMD due to the operation (Kroger et al. 1996). During surgery, bone is removed and compacted due to rasping and insertion of the stem. The reference measurement is of importance because it influences all later results. Aamodt (2004) presented 2-year dual-energy X-ray absorptiometry (DXA) results, with 23% bone loss in Gruen zone 7 for the ABG-1 stem. Van der Wal et al. (2008) reported 2 patient groups with 12% and 15% reduction in BMD in zone 7 for the same femoral stem. The only obvious difference in these 2 studies was the timing of the first measurement. Van der Wal performed the baseline measurement at 10 days postoperatively while Aamodt performed the first postoperative measurement 3–5 days after the operation. Rapid bone loss from day 3–5 to day 10 could therefore have explained the difference in bone loss at 2 years.

It is not fully known whether the bone loss starts immediately after the operation or after a few weeks. In the early postoperative period, BMD might change because of disuse atrophy (McCarthy et al. 1991) or because of the trauma to the bone (Karlsson et al. 2000). We hypothesized there is a rapid bone loss in the first days after operation, which would be an important source of bias to postoperative reference measurements.

Patients and methods

We included 23 patients (15 women) who were operated with an uncemented HA-coated Corail stem (DePuy International Ltd., Leeds, UK). The inclusion criterion was indication for THA with an uncemented stem. Exclusion criteria were infection, revision arthroplasty, marked bone loss, medication with bone-active drugs, or severe morbidity. Mean age at time of

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Table 1. The coefficient of variation (CV%) of the BMD measurements in different Gruen zones and overall

	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Overall
1 day	1.5	3.0	3.4	0.8	2.2	0.9	1.0	2.1
5 days	1.2	2.9	1.9	1.1	2.6	1.7	2.0	2.4
14 days	0.9	1.7	1.3	0.7	0.7	0.9	1.8	1.7
3 months	1.2	1.0	1.1	1.0	1.0	1.1	1.0	1.4
12 months	2.1	1.8	1.9	3.1	3.0	2.7	5.1	2.0

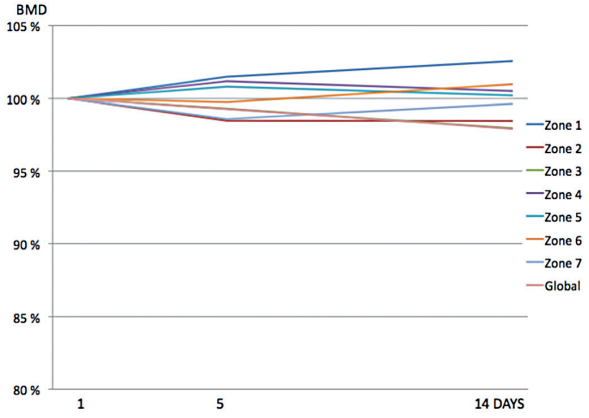

Figure 1. Changes in bone mineral density (BMD) in different regions over the first 14 days after insertion of an uncemented femoral stem. Results are medians, given as percentages of the first postoperative value.

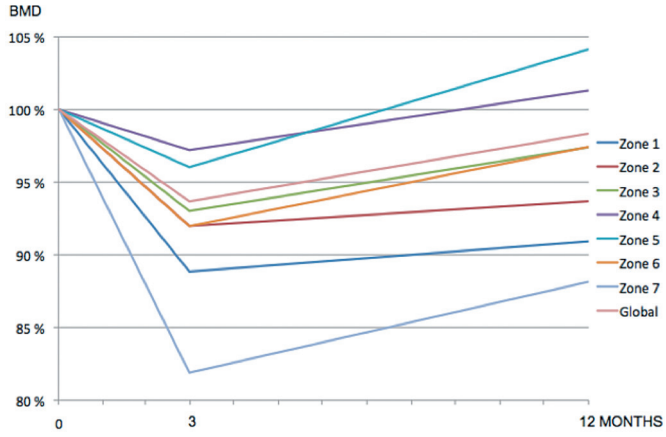

Figure 2. Changes in bone mineral density (BMD) in different regions during the first year after insertion of an uncemented femoral stem. Results are medians, given as percentages of the first postoperative value.

operation was 64 (34–82) years. Recruitment was through informed consent. The Norwegian Data Inspectorate and the regional ethics committee approved the study, and it was carried out according to the Helsinki declaration.

BMD was measured with DXA by experienced technicians. 2 different DXA machines were used in 2 different institutions (Prodigy; Lunar, Madison, WI and Hologic QDR; Hologic Inc., Bedford, MA). Each patient was measured on the same machine on all occasions. The patients were placed supine on the scan table with a foot support to achieve a standard rotation of the hip. Orthopaedic software (Lunar version 1.2 and Hologic QDR version 12.3) was used to analyze periprosthetic BMD in 7 regions of interest (ROIs). The ROIs were based on the Gruen zones. The patients were measured 1–2 days postoperatively, and on days 5 and 14. For follow-up, they were measured after 3 months and 1 year. 16 patients underwent all 5 measurements.

Statistics

The results were calculated as change in percent. Differences were compared by Wilcoxon signed rank test (non-parametric) using PASW statistics software version 18.0 (SPSS). To calculate precision error, all examinations were repeated on the same day with repositioning between the scans. The differences between these paired BMD measurements were used to calculate the coefficient of variation (CV) for each ROI: $CV\% = 100 \times [(\delta/\sqrt{2})/\mu]$ for each ROI, where δ represents the standard deviation of the difference between the paired BMD measurements, and μ is the overall mean of all the BMD measurements for each individual ROI.

Results

The precision (CV) of DXA measurements varied from 0.8% in Gruen zone 4 to 5.1% in zone 7. Mean CV was 1.8% (Table 1).

There was no change in BMD in the first 2 weeks postoperatively (Figure 1). Between 14 days and 3 months, there was a mean bone loss of 8%, ranging from 18% in zone 7 to 4% in zones 4 and 5 ($p < 0.05$ for all zones). There was restoration of bone in all zones from the 3-month to the 12-month follow-up (Figure 2). This restoration was from 2% to 8% and was statistically significant in zones 2–6 ($p = 0.02$, $p < 0.001$, $p < 0.001$, $p = 0.001$, and $p = 0.05$). The BMD decreased most in zone 7: by 18% after 3 months (Table 2).

Table 2. Median bone mineral density in different regions after insertion of an uncemented femoral stem. Results are percent (range) after 5 days, 14 days, 3 months, and 12 months

	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Global
5 days	101 (95–110)	98 (92–101)	99 (89–122)	101 (98–107)	101 (91–108)	100 (91–117)	99 (89–113)	99 (95–120)
14 days	103 (96–107)	98 (90–106)	98 (90–125)	101 (96–112)	100 (91–107)	101 (92–109)	100 (91–109)	98 (90–111)
3 months	89 (77–109)	89 (74–103)	93 (80–137)	97 (94–107)	96 (82–104)	92 (79–120)	82 (70–101)	94 (88–110)
12 months	91 (73–102)	94 (84–111)	97 (90–139)	101 (95–114)	104 (93–127)	97 (82–114)	88 (66–100)	98 (91–114)

Discussion

We found similar BMD values during the first 14 days after implantation of an uncemented femoral stem. Baseline measurement for bone remodeling studies with DXA can therefore be done at any time in this interval.

Bone changes around implants have been an area of continued interest. Aseptic loosening is thought to be the consequence of bone loss (often attributed to stress shielding) and an inflammatory process induced by foreign body particles (Bobyn et al. 1992, Van Rietbergen et al. 1993, Hoenders et al. 2008). The most informative and frequently used way to present periprosthetic bone remodeling is relative change as a function of time. Since there are different forms of bias related to use of preoperative measurements, such as disuse atrophy, sclerotic bone and peroperative bone loss, the recommended baseline is the first postoperative measurement (Venesmaa et al. 2001). Van der Wal et al. (2008) stated that studies comparing BMD after operation with THA should be matched for preoperative BMD and sex. A correlation between preoperative BMD and postoperative bone loss indicates that the lower the BMD before operation, the higher is the bone loss after the operation (Venesmaa et al. 2003, Rahmy et al. 2004, Alm et al. 2009). Kiratli et al. (1996) defined 4 ROIs in the proximal femur of the operated hip and did not find any correlation between preoperative BMD and the postoperative bone-remodeling pattern. Their first postoperative measurement, done less than 5 days after the operation, showed an increased BMD in all 4 ROIs. All values almost returned to baseline within 1 month.

The most marked postoperative bone loss takes place in the first months after the operation. Bone loss of up to 21% has been reported in the first 3 months in Gruen zones 1 and 7 (Boden and Adolphson 2004). As in our study, Trevisan et al. (1997) also found an increase in BMD in the greater trochanter early after the operation. They took the first postoperative measurements at 2 months and compared these values with preoperative values. BMD appears to stabilize after approximately 6 months (Kroger et al. 1997). The main reason for bone loss is thought to be partial weight bearing and stress shielding. Boden and Adolphson (2004) compared BMD in 20 patients randomized to partial or full weight bearing. The group with partial weight bearing had lost more bone in Gruen zones 1, 4, and 5 after 3 months than those with full weight bearing. Differences in BMD between study groups appear to level off with time. In the material of Boden and Adolphson, the difference due to weight bearing only remained for 2 years in zone 1. Thien et al. (2010) compared a polymethyl methacrylate-coated (PMMA-coated) stem, a polished stem, and a matte stem. Initially, the polished stem lost less bone and subsided more then the other two. After 5 years of follow–up, there was no difference. In our own study on Taperloc stems (Bøe et al. 2011), there was a significant difference in bone remodeling in the major trochanter between 2 different hydroxyapatite-coated stems during the first 2 years.

In addition to having reliable reference measurement, longitudinal studies depend on reproducibility. Rotation of the femur appears to be the most significant factor affecting reproducibility (Cohen and Rushton 1995). Repositioning of the patient between 2 measurements on the same day should give us reliable feedback on the precision of DXA measurements. In our study, a coefficient of variation below 5% indicated good precision, and daily scanning of a phantom allowed us to check for drift of the DXA machines.

Another factor influencing BMD around implants is operation technique. Compaction is a bone-saving technique compared to conventional bone-removing techniques by a rasp with similar shape as the stem. Using a dog model, Kold et al. (2005a) showed that operation with compaction around an HA-coated implant increased the peri-implant bone density and bone implant contact. This indicates that compaction may be an advancement in human joint replacement to enhance initial fixation. Even though compaction represents autograft of non-vital bone, which is resorbed over time, the fixation does not appear to be inferior after bone resorption (Kold et al. 2005b). To our knowledge, the technique has not been tested in a human clinical trial. Perhaps compaction is the reason for increased BMD immediately after surgery, since most of the rasps that are used can probably both compact and remove bone. It is of some concern that the risk of femoral fractures increases with compaction (Kold et al. 2003).

Bone remodeling after implantation of prostheses may be compared to remodeling after partial weight bearing because of fractures. Eyres and Kanis (1995) found a definite and persistent loss of BMD in the distal tibia 5–11 years after fracture. At the fracture site, there was sclerosis and a higher BMD than

on the control side. In that material, there was no improvement in BMD with weight bearing. Fractures sustained in childhood did not lead to bone loss in the distal tibia. There have been several publications indicating that bone loss may be the result of a fracture, and not necessary the cause of it (Andersson and Nilsson 1979, Eyres and Kanis 1995, Karlsson et al. 2000). Karlsson et al. (2000) published BMD results from both legs, both hips, spine, and total body in patients who were operated with tibial osteotomy for localized medial osteoarthritis. They found substantial bone loss in the whole body, the spine, and the contralateral hip after 9 and 15 months. In the leg with osteotomy, the bone loss was significant in the distal femur after 4 months (compared to baseline) and in the shaft of the tibia after 9 and 15 months. The conclusion from that work was that bone loss following an osteotomy is rapid, affects both fractured and unfractured bones, and is not completely reversible. The same mechanisms may be responsible for the bone remodeling seen after implantation of prostheses, but the exact reason for this "post-traumatic" bone loss is unknown.

BB wrote the protocol and designed the study, performed the DXA analysis, wrote the manuscript, and did the statistical evaluation. LN designed the study, included patients, and helped write the manuscript. TH included, followed, and operated on most patients.

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A prospective randomized study comparing electrochemically deposited hydroxyapatite and plasma-sprayed hydroxyapatite on titanium stems

55 hips followed for 2 years with RSA and DXA

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Background and purpose **Plasma-sprayed hydroxyapatite (HA) is a successful coating for fixation of uncemented femoral stems. There may be alternative coatings with advantages in bone remodeling and transport of bone-active substances. We investigated whether an electrochemically deposited hydroxyapatite, Bonemaster (BM), might be a safe alternative in total hip arthroplasty. Our hypothesis was that the new coating would not be inferior to the conventional one.**

Patients and methods **50 patients (55 hips) were included. The stem was tapered and porous-coated proximally. On top of the porous coating was either HA or BM. Patients were evaluated postoperatively and after 3, 6, 12, and 24 months to measure fixation by radiostereometric analysis (RSA), bone mineral density by dual-energy X-ray absorptiometry (DXA), and conventional radiography. Clinical evaluation was performed with Harris hip score and Oxford hip score, both preoperatively and after 2 years.**

Results **After 2 years, the stems had subsided 0.25 (HA) and 0.28 (BM) mm and there were no statistically significant differences between the groups in any direction, regarding both migration and rotation. The BM group retained significantly more bone than the HA group in Gruen zone 1 during the first 2 years. The Harris and Oxford hip scores were similar in both groups.**

Interpretation **Electrochemically deposited hydroxyapatite on an uncemented stem does not appear to be inferior to plasma-sprayed HA regarding clinical and radiological results, bone remodeling, and micromotion after 2 years follow-up.**

Aseptic loosening is the most frequent complication of total hip arthroplasty (THA) (Havelin et al. 2000). The long-term survival is thought to depend partly on bone loss or osteolysis in the proximal femur after insertion. Plasma-sprayed hydroxyapatite (HA) coatings appear to give effective fixation in the femur (Hallan et al. 2007). Alternative coatings may, however, influence bone remodeling around the prosthesis and may function as a carrier of bone-active substances.

Bonemaster (BM) (Bonemaster is a registered trademark of Biomet Europe) is an electrochemically deposited hydroxyapatite (EDHA) coating (Rößler et al. 2002). This technique makes it possible to add biological substrates such as antibiotics or adhesion peptides to the coating and still keep the coating very thin compared to plasma-sprayed HA.

The thickness of a hydroxyapatite coating is a compromise between the mechanical properties and dissolution of the coating. A thinner coating minimizes the potential of particle shedding during insertion. Fewer particles in the joint mean less third-body wear and less periprosthetic osteolysis (Peters et al. 1992, Shanbhag et al. 1994, Campbell et al. 1995, McKellop et al. 1995). Thinner coatings also lower the risk of HA delamination and preserve the porosity of the underlying metallic coating of the implant. The irregular implant surface increases the surface area, providing a greater contact and ingrowth area (Sewing et al. 2002). EDHA, as in Bonemaster, forms a needle-like porous structure (Rößler et al. 2001) and enhances early-stage fixation between implant and bone (Ban et al. 1997).

We designed a prospective randomized trial to compare conventional plasma-sprayed HA with electrochemically deposited HA after insertion of an uncemented femoral stem. This is the first clinical trial with the Bonemaster coating. We hypothesized that implants with Bonemaster would achieve the same degree of stability and bone remodeling, and the same clinical outcome as implants with traditionally plasma-sprayed HA.

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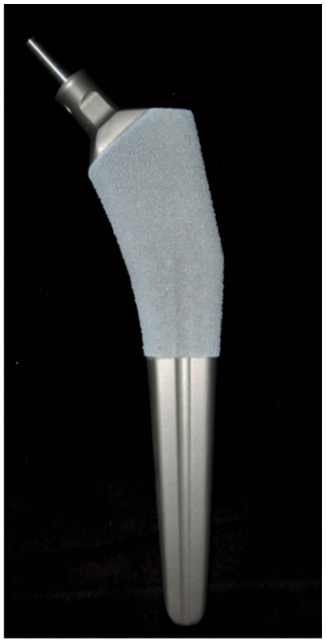

Figure 1. Taperloc stem coated with Bonemaster.

Patients and methods

50 patients (31 of whom were women; 55 hips) with noninflammatory end-stage osteoarthritis of the hip participated. Inclusion criteria were health condition expected to allow follow-up for 10 years and anatomy compatible with use of a standard implant. Exclusion criteria were infection, revision arthroplasty, marked bone loss, and severe morbidity. Mean age at the time of operation was 63 (27–81) years. From December 2003 through June 2005, patients underwent THA with the Taperloc uncemented stem (Figure 1), a 28-mm cobalt-chrome modular head and the SHP cemented cup. (The stems were manufactured by Biomet UK Healthcare Ltd.; all other components were from Biomet, Warsaw, IN). Both hips of 5 patients were included. Recruitment was by informed consent and the patients were on our waiting list for THA. The Norwegian Data Inspectorate and the regional ethical committee approved the study and it was carried out in line with the Helsinki declaration.

The patients were randomized (with sealed envelopes) to a stem with either plasma-sprayed HA or Bonemaster. 31 hips were operated with BM-coated stems and 24 with plasma-sprayed HA-coated stems. After a power analysis performed during the study, we ended the inclusion after recruiting 55 hips, leaving 45 envelopes unopened. 1 patient was excluded because of a periprosthetic fracture. 2 patients have subsequently been revised because of loose cups. These 2 patients have been followed with measurements of the stem after their revisions. 1 patient was reoperated after 5 weeks with soft tissue revision and change of femoral head because of infection, but was kept in the study.

4 orthopedic consultants in 2 hospitals operated the patients using the modified Hardinge approach.

The Taperloc stem was manufactured from forged titanium alloy, Ti-6Al-4V. It had a tapered form and was porous-coated proximally. On top of the porous coating, the stem was coated with either plasma-sprayed HA or electrochemically deposited hydroxyapatite (BM). Plasma spraying of HA is a high-temperature process designed to deliver slightly molten $Ca(PO_4)_2$ granules of µm size onto metal surfaces. The process was first described by de Groot et al. (1987). The specifications for the implants in this study were according to the manufacturer: 50-micron thick HA coating (Ca/P ratio: 1.67), a mean surface roughness of 41 microns, a maximum roughness depth of 445 microns, and 62% crystallinity. The electrochemically deposited hydroxyapatite coating was performed in an electrolyte solution near physiological conditions (pH 6.4, 37°C), consisting of 1.67 mM $CaCl_2$ and 1 mM $NH_4(H_2PO_4)$ in equal volumes with the implant polarized in cathode galvanostatic mode (–75 A/m2). The layer consisted of 70–72% crystalline HA with the balance being amorphous, and with a thickness of 5 µm and a Ca/P ratio of 2.0. The time taken to apply this form of HA coating is much slower than that of HA applied by plasma spray, and is typically 75 min per implant. Details of preparations, characteristics, and appearances of coatings are as described by Rößler et al. (2002) and Sewing et al. (2004).

On the acetabular side, we used SHP—an all-poly gamma-irradiated (ArCom) cemented cup—inserted with Palacos (Schering-Plough) gentamycin-containing cement.

Bone mineral density (BMD) was measured by experienced technicians using DXA. 3 different DXA machines were used (Prodigy and Expert; both from Lunar, Madison, WI—and Hologic QDR; Hologic Inc., Bedford, MA). The patient was placed supine on the scan table with a foot support to achieve standard rotation of the hip. Orthopedic software (Lunar version 1.2 and Hologic QDR version 12.3) was used to analyze periprosthetic BMD in 7 regions of interest (ROIs). The ROIs were based on the Gruen zones. The patients were measured within a few days postoperatively (mean 5.8 days) and after 3, 6, 12, and 24 months. 30 patients treated at "hospital A" were measured with a Lunar Expert densitometer until January 1, 2005 and later with a Hologic densitometer. 25 patients treated at "hospital B" were measured with a Lunar Prodigy densitometer. We calculated a transformation formula between Lunar Expert and Hologic values based on measurements from 5 of the patients included. These 5 patients were measured twice on both densitometers, and on the same day. Assuming linearity between the 2 machines, the best fit was found using the formula $BMD_{Lunar} = 0.789 \times (BMD_{Hologic}) + 0.2089$. Because this transformation of values represents a bias in the patient group from hospital A, we performed statistical analysis on the total number of patients, and on the patients from hospital B separately.

To calculate precision error (the coefficient of variation, CV%) of the 3 densitometers, 130 examinations were repeated on the same day, with repositioning between the scans (Table 1).

Table 1. Coefficient of variation (CV) in per cent for the 3 densiometers used in 7 Gruen zones

Zone:	1	2	3	4	5	6	7
Expert	2.0	1.5	2.0	1.4	2.3	2.3	2.8
Hologic	0.5	5.8	1.5	0.6	1.5	1.1	0.8
Prodigy	2.6	2.1	1.7	3.6	2.2	5.1	2.9

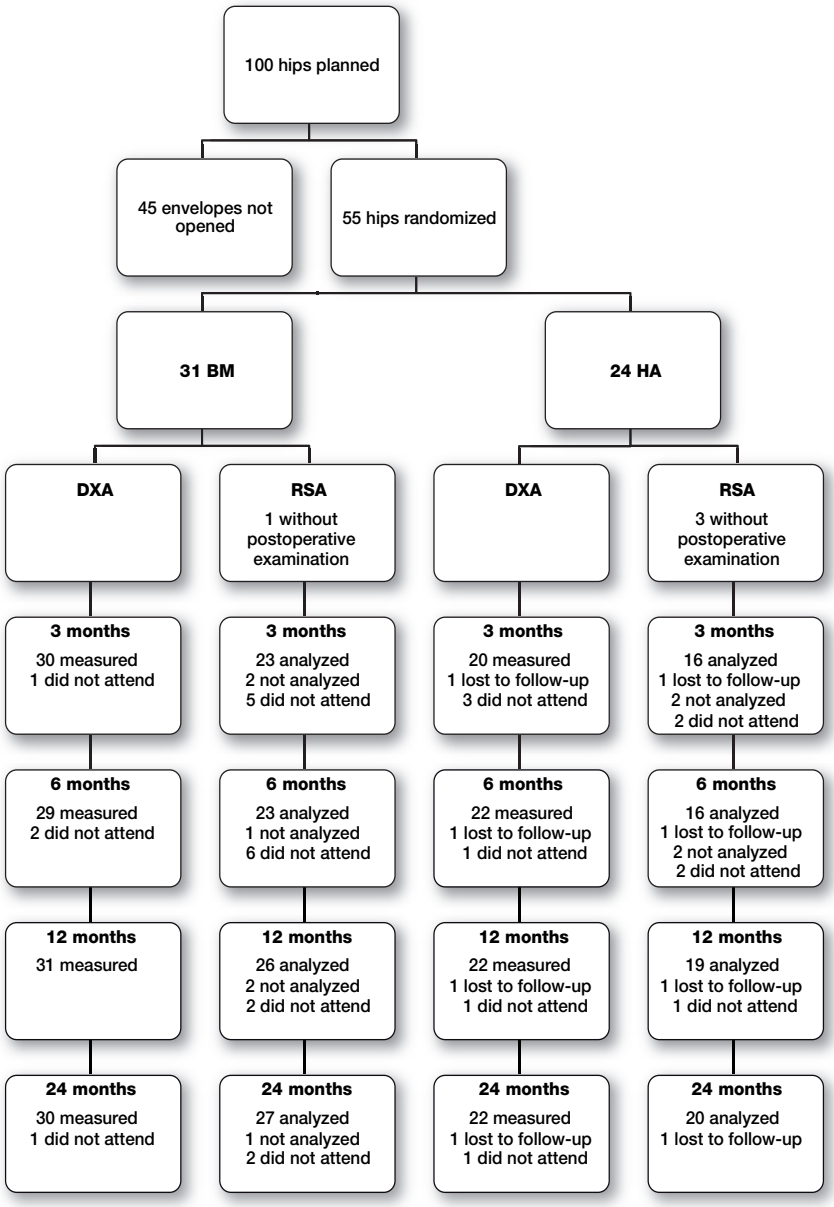

Figure 2. Flow chart of the patients with DXA and RSA measurements. The patient lost to follow-up had an HA-coated stem inserted at hospital A. 17 BM-coated stems were inserted at hospital A and 14 BM-coated stems were inserted at hospital B. 13 HA-coated stems were inserted at hospital A and 11 HA-coated stems were inserted at hospital B. Those patients who were not analyzed by RSA did not meet the criteria of a maximum condition number of 100 or mean error of less than 0.3.

RSA

During the operation 7-8 tantalum markers of 1.0 mm were inserted into the proximal part of the femur. The manufacturer had attached 3 tantalum markers to the femoral stem, 1 to the shoulder, 1 to the neck and 1 to the tip. We also computed the position of the femoral head centre. Radiostereometric examinations were done at approximately 7 days, 3 months, 6 months, 1 year, and 2 years after the operation. We evaluated migration of the gravitational centre of the segment which was defined by the stem markers and the centre of the femoral head. Migration was measured along the cardinal axes. Stem rotations were measured as rotations of that segment around the same axes. Analyses were performed using UmRSA (Digital measurement 6.0 RSA Biomedical, Umeå, Sweden). In 4 cases the quality of the postoperative stereoradiographs did not allow a proper evaluation. 1 patient was lost to follow up, 2 did not meet and 1 patient was excluded from the 2 years analysis because of high condition number. 47 patients were to be analyzed at 2 years with mean error below 0.3 and condition number below 100 (Figure 2). 83 examinations were repeated the same day to calculate the precision of our measurements. RSA results are presented as mean values with standard error of mean (SEM).

Conventional radiography

Anteroposterior and lateral examinations were done preoperatively, postoperatively, and after 3, 6, 12, and 24 months. 2 surgeons evaluated the radiographs. The parameters registered were implant position, radiolucency or lysis, calcar resorption, heterotopic bone formation, trabecular remodeling, cyst formation, pedestal formation, and visible migration. Radiolucent lines were considered to be present if they were > 1.0 mm and occupied more than 50% of the interface in each Gruen zone.

Clinical evaluation

Harris hip score (Harris 1969) and Oxford hip score (Dawson et al. 1996) were evaluated preoperatively and after 2 years.

Statistics

The statistical analysis of BMD and RSA results to compare Bonemaster to HA was done using non-inferiority testing comparing areas (SPSS for Mac version PASW 18.0). The BMD results were expressed as percentages (mean) with standard deviation (SD). RSA results were signed values (mean) with

Table 2. Periprosthetic changes in bone mineral density around hydroxyapatite- (HA-) and Bonemaster- (BM-) coated Taperloc stems measured by dual-energy X-ray absorbtiometry (DXA). Results are given in percentage (standard deviation) of postoperative values after 3 months, 6 months, 1 year, and 2 years

Gruen zone	n	3 months	n	6 months	n	1 year	n	2 year
1 Bonemaster	30	92 (19)	29	94 (25)	31	90 (26)	30	87 (19)
HA	20	83 (14)	22	79 (13)	22	76 (15)	22	79 (18)
2 Bonemaster	30	89 (10)	29	92 (8)	31	90 (10)	30	87 (14)
HA	20	90 (10)	22	90 (8)	22	89 (9)	22	86 (10)
3 Bonemaster	30	93 (7)	29	96 (6)	31	94 (8)	30	90 (12)
HA	20	94 (5)	22	96 (5)	22	95 (7)	22	92 (9)
4 Bonemaster	30	95 (5)	29	95 (6)	31	94 (5)	30	90 (9)
HA	20	96 (5)	22	95 (4)	22	94 (6)	22	90 (7)
5 Bonemaster	30	94 (7)	29	97 (7)	31	96 (9)	30	90 (11)
HA	20	97 (5)	22	97 (6)	22	93 (10)	22	88 (12)
6 Bonemaster	30	93 (9)	29	94 (8)	31	94 (9)	30	89 (11)
HA	20	94 (7)	22	86 (23)	22	90 (10)	22	88 (9)
7 Bonemaster	30	82 (13)	29	77 (14)	31	73 (15)	30	70 (16)
HA	20	83 (9)	22	77 (11)	22	73 (12)	22	69 (13)

SEM. The DXA and RSA results were not normally distributed. The 2 groups were compared with the Mann-Whitney U-test. Changes in DXA, postoperatively to the 2-year follow-up, were analyzed with Wilcoxon signed rank test.

A power analysis was not performed before the study started. Based on an estimated clinically important difference in BMD of 10% (SD 10), stem migration of 0.6 mm (SD 0.6), and stem rotation of 0.7 degrees (SD 0.7) between groups, the sample size calculation indicated 17 patients would be required in each group to achieve 80% power at the 0.05 significance level. Due to the risk of patient dropout, at least 24 patients were included in each group.

Results

DXA

After 2 years, there was bone loss compared to the postoperative values in both groups in all regions around the stem ($p < 0.05$), which was most pronounced in Gruen zones 1 and 7 (Table 2). With non-inferiority testing between the 2 groups, we had to reject the null hypothesis (that Taperloc would function equally well with Bonemaster and HA) for zone 1. Comparison of the areas under the graph showed a significant difference between HA and BM in zone 1 after 2 years ($p = 0.01$). The bone loss was less in the Bonemaster group. Because of the possible bias with the transformation formula used in hospital A, we also performed the analyses with the results from hospital B alone. We found the same as for the whole group: rejection of the null hypothesis in zone 1 ($p = 0.01$). For all other Gruen zones, the null hypothesis was retained.

RSA

The precision of our measurements was 0.11 mm for subsidence and 0.66 degrees for retroversion. The migration pattern for both stems showed that they moved during the first 3 months after surgery and then stabilized (Figures 3 and 4). The mean (SD) subsidence for the center of the stem after 2 years was 0.28 (0.47) mm for BM and 0.25 (0.69) mm for HA (Figure 3). The stems with Bonemaster moved mean 0.46 (0.73) degrees in retroversion compared to 0.17 (0.83) degrees for the HA-coated stems ($p = 0.2$) (Figure 4). Both groups had retroversion that was lower than the precision in this direction (0.66). With non-inferiority testing, there were no significant differences between groups in any migration or rotation after 2 years.

Clinical results

Harris hip score increased from 55 (pain score 20) preoperatively to 95 (pain score 41) after 2 years in the Bonemaster group, which was almost similar to the increase from 52 (18) to 89 (38) in the HA group. Oxford hip score improved from 39 preoperatively to 16 after 2 years in the BM group and from 35 to 19 in the HA group. The differences after 2 years were not statistically significant.

There were no radiolucent lines around the stems after 2 years. 1 patient was excluded because of a periprosthetic fracture 6 weeks after the operation. 2 patients in the BM group were revised after 10 and 13 months because of cup loosening. They were both revised because of pain, and we continued to follow the femoral component in the study. Another patient (in the BM group) had a postoperative infection and was revised with soft tissue debridement and irrigation. Treatment of the infection was successful and the patient continued in the study.

RSA and BMD results were analyzed both with and without the reoperated patients included, with no significant changes in the results.

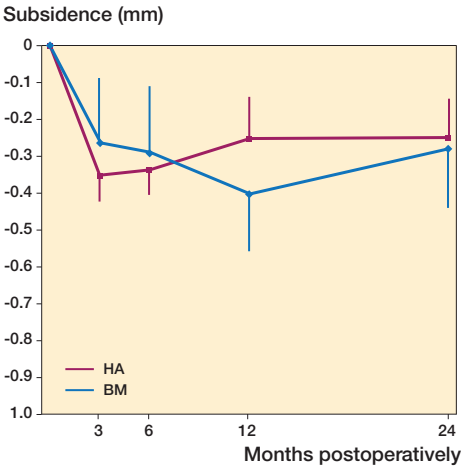

Figure 3. Subsidence (0.25 (HA) and 0.28 (BM) mm in the first 2 years) after implantation of hydroxyapatite- (HA-) and Bonemaster- (BM-) coated Taperloc stems, analyzed by radiostereometric analysis (RSA). Results are given in mm with standard error of the mean after 3 months, 6 months, 1 year, and 2 years.

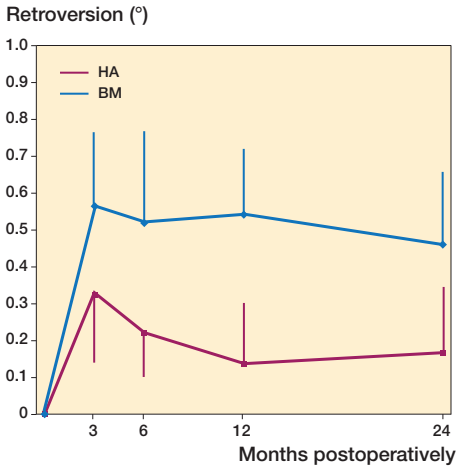

Figure 4. Retroversion of hydroxyapatite- (HA-) and Bonemaster- (BM-) coated Taperloc stems after 2 years, analyzed by radiostereometric analysis. Results are in degrees with standard error of the mean.

Discussion

Our study was started as a safety study of a new electrochemically deposited HA coating. The null hypothesis was that Taperloc would function equally well with Bonemaster and HA. Our results show that Bonemaster-coated stems do not function in an inferior way to stems coated with plasma-sprayed HA after 2 years.

The most recent publication for the Taperloc stem without any HA coating (McLaughlin and Lee 2008) describes good long-term results for aseptic loosening with 87% survival after 20 years. The Taperloc is therefore a good stem for safety studies of new technology.

We already knew that HA coating of a porous surface is an excellent fixation method. Both Karrholm et al. (1994) and Soballe et al. (1993) showed that there is less subsidence with HA-coated stems than with porous-coated stems. The question is therefore "do we need Bonemaster?". The total number of cementless procedures has increased in recent years. A benefit of a coating placed on the stem by galvanic electrolysis is that it can act as a carrier for other substrates. Infections remain a critical issue in total joint arthroplasty. Antibiotics added to the coating would probably lower the infection rate. Alt et al. (2006) demonstrated a lower infection rate in a combined gentamicin-HA group than in an ordinary HA group in a rabbit model.

Osteolysis and bone loss may lead to loosening of the implant or periprosthetic fractures. We suggest that some of the proximal bone loss is due to the surgical trauma from cutting of the neck and preparing the proximal femur to receive the prosthesis. We found less reduction in bone density in the Bonemaster group than in the HA group in Gruen zone 1 during the first 2 years. We found no difference in zones 2, 6, and 7, which are also regions with BM coating. Perhaps the initial difference between the 2 groups was detected in zone 1 because this is an area dominated by trabecular bone. Higher bone density values in the Bonemaster group may indicate a higher degree of bone turnover in trabecular bone in this group. An expected result of DXA measurements after implantation of a hip prosthesis is a marked bone loss initially, and then restoration of bone (Trevisan et al. 1997, Wixson et al. 1997, Karachalios et al. 2004). We have not seen any restoration of bone around the Taperloc stem during the first two years, but bone loss from 7% (zone 3) to 31% (zone 7) is acceptable compared to other stems. It remains to be seen whether the bone loss would continue. For prostheses with satisfactory results, the bone loss is often limited to the proximal zones. In patients with early aseptic loosening, a different pattern of bone remodeling with reduction along the entire stem has been found (Boden et al. 2004). Scott and Jaffe (1996) predicted that higher BMD indicates better ingrowth of bone to the implant. In that case, Bonemaster leads to faster bone ingrowth than HA. This was not reflected by better stability early on, however, as measured by RSA. In an animal study with mechanical pull-out testing, Yang et al. (2008) showed that roughened titanium implants had better initial fixation to bone when they were coated with electrochemically deposited HA than when they only had roughened titanium on the surface.

Another experimental study has shown that plasma-sprayed HA accelerates the early-stage mineralization (< 7 days) of bone more than EDHA coating (Wang et al. 2006). However, EDHA appeared to have resulted in better mechanical integration between the coating and mineralized tissue. Plasma-sprayed HA and EDHA were indistinguishable later (14 days) regarding the mineralized tissue ratio and microstructure they induced in vivo.

Results for the patients measured on the same DXA machine during the entire study were the same as for the whole group.

We therefore consider the values to be reliable for comparison, although a change of DXA machine at one institution complicated calculation of bone remodeling.

The amount of acceptable subsidence probably varies between different stem designs and fixation methods. Karrholm et al. (1994) showed that the amount of subsidence after 2 years was the best predictor of later revisions in cemented stems. The cut-off values for the probability of revision to exceed 50% and 95% were 1.2 mm and 2.6 mm of subsidence after 2 years. In a study with HP-Garche uncemented stems, Wykman et al. (1988) reported 0.6–3.9 mm of subsidence in 7 of 8 stems after 2 years. In a later report, the same group reported that 13 of 78 HP-Garche stems (17%) had to be revised in less than four years (Wykman et al. 1991).

Wykman and Lundberg (Wykman and Lundberg 1992) presented an RSA study of 9 patients with porous-coated Taperloc stems. 3 stems had subsided 0.7–0.9 mm after 2 years, and the mean subsidence after 2 years was 0.44 mm. Compared to earlier studies our results thus indicate that concerning subsidence, HA coating of the Taperloc stem is beneficial.

In our trial, the stem subsided in the three first months postoperatively and then stabilized. This migration pattern has also been shown with other HA-coated implants. Thien et al. (2007) published the same pattern of subsidence for 43 ABG stems. For the clinically proven Corail stem, Campbell et al. (2009) documented more subsidence (0.58 mm) than for Taperloc over the first 2 years, using RSA analysis. Corail had the same migration pattern, however, with stability after 6 months. As both Corail and Taperloc have good long-term clinical results (Hallan et al. 2007), it appears that subsidence during the first months and then stabilization within a year is typical for these designs of HA-coated uncemented implants. This might be explained by the ability of hydroxyapatite to close the gap between bone and implant (Overgaard et al. 1997). Long-term follow-up will be necessary to evaluate the effect of electrochemically applied HA on long-term fixation. Further studies are required to investigate whether electrochemically deposited HA combined with antibiotics might lower the infection rate.

In conclusion, the Taperloc stem with Bonemaster does not appear to be inferior to the Taperloc stem with plasma-sprayed HA, concerning clinical and radiological results, bone remodeling, and micromotion—at least up to 2 years.

BB did the clinical follow-up, RSA and DXA analysis, wrote the manuscript and performed the statistical evaluation. LN designed the study, operated, and helped with the statistics and writing of the manuscript. SF designed the study with LN, operated, and followed many of the patients. TH included, followed, and operated most of the patients. SR supervised the RSA analysis and helped in writing the manuscript.

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Osteoinduction by implantation of titanium discs with two different hydroxyapatite coatings in rabbit muscles

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Abstract:

Objectives:

An experimental rabbit model was used to test the hypothesis that implanting titanium discs with a thin electrochemically deposited hydroxyapatite coating (Bonemaster®) in muscles would not induce new bone formation.

Methods: 4 titanium discs with different surface and coating (A. Grit blasted + Bonemaster®, B. Porous coating, C. Porous coating + Bonemaster® and D. Porous coating + plasma sprayed hydroxyapatite) were implanted in 12 female rabbits. Six animals were killed after 6 weeks and 6 animals after 12 weeks. The implants with surrounding tissues were embedded in methyl methacrylate and grinded sections were stained with Masson-Goldners trichrome and examined by light microscopy of coded sections.

Results: Small amounts of bone were observed scattered along the surface of 4 of 11 grit blasted implants coated with Bonemaster®. We also found small bone fragments around 5 out of 12 implants coated with porous titanium and around 1 out of 12 porous coated surfaces with Bonemaster®. No bone formation could be detected around porous coated implants with plasma sprayed hydroxyapatite.

Conclusion: Bonemaster® coating on a titanium surface is to some degree osteoinductive in muscles.

Key words: Osteoinduction, hydroxyapatite, Bonemaster®, implant surface, porous titanium.

Article summary:

Article focus

- Is it possible to avoid osteolysis by improving implant surfaces?
- How can we prove hydroxyapatite to be osteoinductive, not only osteoconductive?
- Is Bonemaster® osteoinductive in muscle?

Key messages

- Implants coated with Bonemaster is proven to give higher bonedensity in trabecular bone than implants plasmasprayed with hydroxyapatite.
- Implants coated with Bonemaster induced formation of bone in muscle.
- Porous coating is osteoinductive without ceramic coating.

Strenghts and limitations of this study

- When implanting in muscle the researcher can be sure the visible bone is induced.
- It is hard to prepare the histological sections thin enough when using metal implants
- The amounts of bone were small in each section. There might be better ways to prove the amount of bone.

Introduction

Titanium alloy is frequently used as material in orthopedic implants. The degree of surface roughness on the micro and macro levels as well as the chemical composition of the implant coating are of importance for bone-implant integration (1). Long time survival of uncemented total hip replacement is dependent upon early implant fixation securing early stability (2). Rough surfaces are considered beneficiary for implant fixation while smooth implant surfaces are more likely to induce fibrous encapsulation that might prevent bone ingrowth. Experimental data show that hydroxyapatite (HA) may enhance bone conduction around titanium implants when HA is plasma sprayed on the implant (3). Plasma spraying results, however, in a thickness of the coating that implies smoothening and closure of the titanium porous surface. Bonemaster® is a new electrochemical deposited hydroxyapatite coating that is only 5 microns thick (Bonemaster® is a registered trademark of Biomet Europe). A thin coating allows the implant to maintain its rough surface as the coating follows the surface of the pores without filling the pits. By combining the known positive effects of HA and a porous surface the approach may represent a step forward in optimizing the conditions for osseointegration of an implant. In support, we found favorable bone remodeling in the major trochanter with a femoral stem coated with Bonemaster® in humans (4). Porous granules of HA implanted subcutaneous have resulted in heterotopic bone formation in dogs (5). Later studies (6) indicated that differences in bone induction depend upon architecture in the surface of ceramic rods. Thus, Yuan and coworkers implanted 2 different types of ceramic rods in dorsal muscles of dogs and found induction of bone

around rods with pores of 200 microns, but no bone around rods with pores of 400 microns (6). In the current study grit blasted titanium discs coated with porous coating, Bonemaster® or HA were implanted in rabbit muscles to disclose possible differences in osteoinductive properties in soft tissue. Our null hypothesis was that discs coated with Bonemaster® do not induce bone formation.

Methods

Animals:

The study was approved by The Norwegian Animal Research Authority (NARA) and conducted in accordance with The Animal Welfare Act of December 20th 1974 and the Regulation of Animal Experimentation of January 15th 1996. The animals were housed in the Laboratory Animal Unit at The Norwegian School of Veterinary Science and the acclimatization period before surgery was 24 days.

Twelve grey female Chinchilla rabbits at the age of 16 weeks and weight between 2900 and 3400g underwent surgery. The surgery was performed during sterile, standardized conditions. Each rabbit had all 4 implants placed intramuscularly in the erector spinae muscles, two on each side of the column approximately 5 cm from each other. The implants were kept in place with a resorbable suture and the skin was closed by intracutaneous suture.

All rabbits were injected 0.8 mL / kg i.m. of a mixture (1:1:1) of Fentanyl (50 µg/mL), Dormicum (Midazolam, 5 mg/mL) and Domitor (Medetomidin, 1 mg/mL). After 5 minutes the rabbits were carried from the cage to the operating theatre. NSAID (Rimadyl 4 mg/kg) was given immediately s.c. Animals were anesthetized with Propovet (Propofol, 10 mg/mL) 0.1 ml / kg i.v. and with any sign of recovery during surgery anesthesia was maintained with a new dose of Propovet 0.1 ml / kg i.v. Lidokel-adrenaline (Lidokain hydrochlorid monohydr. 20 mg, adrenalin tartr. 36 µg) 1 ml / 3 kg was given locally at the site of surgery. Each animal received an injection with 10 ml/kg of NaCl warmed to body temperature infusion s.c. and buprenorphine (Temgesic®) 0.05 mg/kg s.c. after surgery. The animals were then placed on an isolating plate in their cages with a hot water bottle. Injection with buprenorphine was repeated 2 times daily for 2 days. Rimadyl® 4 mg/kg was given s.c. once daily for 2 days after surgery. The rabbits were kept in separate cages for 2 days following surgery. All animals were checked for wound healing and general health condition before they were moved from their single cage to a room with other rabbits. There were no postoperative complications.

Six rabbits were sacrificed with Zoletil vet.® (Virbac®) and Pentobarbital® (pentobarbital natrium 100 mg/mL) after 6 weeks and the last 6 rabbits after 12 weeks. The implants including a brim of surrounding muscle were immediately dissected free and fixed in 4% buffered formaldehyde.

Implants:

Four different implant surfaces was investigated; (A) grit blasted and Bonemaster® (GB-BM), (B) porous titanium coating (PC), (C) porous titanium coating and Bonemaster® (PC-BM), and (D) porous coating and hydroxyapatite (PC-HA). The implants (Biomet, UK) were shaped as discs with a diameter of 10 mm and a height of 2 mm. Following grit blasting the discs show a surface roughness of approximately 1 micron (7). By “porous coating” a layer of small particles is laid onto the metal surface shaping channels or pores increasing the surface area. A mean surface roughness of 47 microns and a maximum roughness depth of 496 microns have previously been reported from this kind of implant produced by the same manufacturer (3). The plasma sprayed HA coating (Figure 1) was approximately 50 microns thick with a mean surface roughness of 41 microns, and a maximum roughness depth of 445 microns. The HA was 62% crystalline with a Ca/P-ratio of 1.67. The electrochemically deposited HA, Bonemaster®, was 5 microns thick and consisted of 70-72% crystalline HA and a Ca/P ratio of 2.0 according to the manufacturer.

Histology

The fixed samples were dehydrated in series of increasing alcohol concentrations and embedded in methyl methacrylate (MMA). Each sample was cut in several sections and grinded to a thickness of 10-20 microns to optimize staining. One sample, grit blasted with Bonemaster®, was destroyed during preparation.

The samples were stained with methylene blue, basic fuchsine or Massons-Goldner's trichrome.

In the latter, green areas showing homogenous or slightly fibrillar structure with osteocyte-like cells inside and/or osteoblast-like cells at the surface were recorded as bone. The occurrence of bone at the surface of the discs was evaluated from coded sections by 3 investigators, one of them an experienced clinical pathologist with special competence in bone pathology.

Statistics

Groups were compared for osteoinduction by Fisher exact test (STATA®, $p < 0.05$ was considered to be significant).

Results

In sections stained with methylene blue and basic fuchsine it was difficult to distinguish between newly formed bone and other types of connective tissue, but in the sections stained with Masson-Goldners trichrome this distinction was possible.

There was variable amounts of fibrous connective tissue around the implants. When present, the amounts of bone was generally small with a patchy distribution. A further quantitation of the amounts of bone was therefore considered less appropriate. Consequently, we decided to present results as presence of "bone" or "no bone". After 6 weeks 3 of the 4 different implant surfaces showed some kind of bone induction. Thus, there were strands of bone running parallel to the implant surface (Figure 2). It was no obvious

morphological difference in amount or maturity in bone tissue between 6 and 12 weeks.

We observed osteoinduction in muscles in 4 out of 11 grit blasted implants coated with Bonemaster®, 5 out of 12 implants coated with porous titanium and in 1 out of 12 implants coated with Bonemaster® and porous titanium (Table 1). There was no bone formation around implants with plasma sprayed HA. The HA coating measured to be approximately 50 microns by the manufacturer, was intact in 10 of 12 samples. In 2 of the samples the coating might have been ripped off during preparation of the sections. In that case, tissue must have been removed too.

Analysed by Fisher's exact test there was a difference ($p=0.02$) for distribution of osteoinduction between the four groups (6 and12 weeks combined). The statistics tells that the distribution among the groups is not likely to be random.

No signs of infection were observed in any of the specimens. However, in a few sections we observed giant cells in close vicinity to the implant as in a foreign body response.

Discussion

We observed bone, albeit in small amounts, on porous or grit blasted surfaces of titanium with the addition of a thin HA coating of Bonemaster® or porous titanium alone. Plasma sprayed HA did not induce bone formation in this experimental model. As far as we know, it has not been shown previously that microlayers of HA can be osteoinductive on a metal surface.

In a recent clinical study of hip prostheses we have compared titanium femoral stems coated with Bonemaster® or plasma sprayed HA. We found

less reduction of bone mineral density around the hip prostheses coated with Bonemaster® compared to HA during the first 2 years after surgery (8). HA has proven to be osteoconductive in implant surgery on dogs (3). HA has also been proven to be osteoinductive in soft tissue in dogs where implanted porous HA granules resulted in heterotopic bone formation after 3 months (5). Barrere and coworkers (9) implanted two different types of metal implants (Ti6A14V and Hedrocel) coated with octacalcium phosphate (OCP) in goats muscles of goats and these scientists observed new bone after 12 and 24 weeks. OCP has a calcium phosphate ratio of 1.33. A porous titanium surface can probably be osteoinductive in itself without ceramics if it is treated chemically and thermally to form an optimal surface structure (10). We found new bone around 5 of 12 samples with porous coating only in our study. Kung et al. presented osteoinduction around titanium implants coated with chitosan-collagen subcutaneously in rats (11). We assume that both physical and chemical properties provided by implants, like the structure and composition of the ceramic, may have an effect on osteogenesis.

The ability to induce bone formation also depends on animal species. In the present study a rabbit model was chosen because the rabbit has bone architecture quite similar to humans. The observation time was set to 6 and 12 weeks based on experience from previous studies (12). The surface coatings were all compared within the same animal. This approach reduced the necessary sample size and the influence of individual factors on the bone formation.

Osteoinduction from hydroxyapatite in dogs and pigs has been reported previously(5, 13). A difference of bone formation between species has also

been shown (13) in that larger animals seem to produce bone where smaller animals don't. Especially dogs seem to exhibit properties of bone formation close to humans. We have not found reports of subcutaneous osteoinduction in rats or mice after implanting pure titanium or titanium with HA. The lack of osteoinduction might be due to the subcutaneous localization. Subcutaneous tissue probably has blood supply and bone morphogenic proteins (BMP) levels different from that of muscles. HA and TCP have been shown to be osteoinductive in muscles, but not in subcututaneous connective tissue in the same mice (14). Osteoinduction around titanium implants has been demonstrated in subcutaneous tissue in rats, those implants were, however, coated with chitosan-collagen (11). Before we started our study we performed a pilot experiment using rats that turned out negative in terms of bone induction. Based on those results and extended literature search we decided to change animal species. The species difference in this aspect may also be due to differences in expression of proteins affecting cell differentiation, like BMPs. Approaches including more bone-like coatings by adding the main organic bone component collagen type 1 to HA have been launched (12). Somewhat surprisingly, the coating with HA and collagen did not show any benefits compared to pure HA.

The osteoconductivity of a HA depends of its crystallinity and stability (15). Like in a fracture site unstable mechanical conditions may lead to formation of fibrous tissue as in non-unions. The rate of the earliest stage of bone formation is influenced by the solubility of the HA (16). The plasma spraying technique seems to stimulate more bone than electrochemically deposited HA during the first days after implantation (17). Higher bone apposition rate has

been shown after 7 days and increased bone growth has been shown after 4 weeks in dog models (18). After this initial period the electrochemically deposited HA has shown the same tensile strength and higher bone volume in the implant vicinity than plasma sprayed HA (12). Yuan and coworkers (19) performed a study where the HA cylinders were implanted in dog muscles for 2.5 years. In this experiment HA induced normal bone with bone marrow in the pores of the HA cylinders. The amount of bone remained stable from 45 days to 2.5 years. The fact that the bone did not disappear or expand after the first induction may be clinically relevant. It remains to see if higher bone volume initially means anything in relation to osteolysis and long time survival of implants. In our experiment the amount of bone formed was low and it did not increase during the period from 6 to 12 weeks. Thus the results may seem of less clinical relevance but in our opinion the relevance relays in proof of a concept.

As indicated above, differences in osteoinduction may be due to local tissue characteristics and thereby the access to osteogenic factors. The area around a fracture or the bone around an implant will be an osteogenic environment where osteogenic factors will be adsorbed triggering osteoinduction. The results of Cheng et al. support this concept (14). Cheng et al. used HE staining for their first light microscopy examinations (2, 4, 6 and 8 weeks) and then Masson trichrome after 12 weeks. We experienced that it was difficult to separate bone tissue from nonmineralized tissue with basic fuchsine and methylene blue and decided to stain with Masson Goldner’s trichrome. Cheng does not describe any problems identifying bone with HE, however we notice that also Daugaard et al. (12) used light green in combination with basic

fuchsine. In our material, the main reasons for needing trichrome staining was due to the limited amount of bone. For later experiments we will consider to supply with immunohistochemistry, electron microscopy or PCR to detect bone.

The four different surfaces in our study may adsorb proteins and cells differently, leading to differences in the possibility of new bone formation. Furthermore, it may be questionable whether the osteoinduction by BMPs and osteoinduction by inorganic materials are related.

Implant surface with fine particles is believed to lead to enhanced ingrowth of bone. Yamasaki and coworkers (5) observed that hydroxyapatite granules with micro pores on their surface could induce bone subcutaneously in dogs. No bone was induced in granules without micro pores. Ronold and coworkers (20) studied the effect of surface roughness on tensile strength. Somewhat surprisingly enhanced ingrowth did not lead to increased tensile strength. The fine particles in their study were 7.5-12.5 microns, approximately the same size as the thickness of Bonemaster® coating (5 microns). In the same study (20) the implants blasted with 180-220 microns particles resulted in markedly increased strength. Probably the newly formed bone needed some undercuts to grow into.

We observed a limited number of giant cells in the proximity of our implants and signs of an inflammatory response have been reported around HA implants before (5). Moreover, Fellah et al investigating cell response to bicalciumphosphat in rat muscles (21) found more giant cells around larger implanted particles (80-200 microns) compared to smaller ones (< 20

microns). However, there were more mononucleated macrophages around the smaller particles.

Resorption of HA coating when implanted in bone is seen to various degrees depending on type of metal surface and composition of HA. On porous surfaces the HA coating tends to be resorbed to a larger extent than on grit blasted surfaces. But where the HA coating is resorbed it might be replaced by bone (22).

In conclusion, we found porous titanium and Bonemaster® on titanium surface osteoinductive in muscle. On the other hand, no osteoinduction was observed around HA coated implants.

Author's contributions:

BB wrote the protocol and designed the study, operated animals, wrote the draft of the manuscript and did the statistical evaluation; LN advised in the design of the study and the histological examination; ROS operated animals, LBS helped with the animal pilot study and the histological examinations, JEE advised in implant preparation and histological examinations, FPR advised in implant preparation and contributed in histologic examinations. All authors contributed to the writing of the manuscript.

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Figure 1

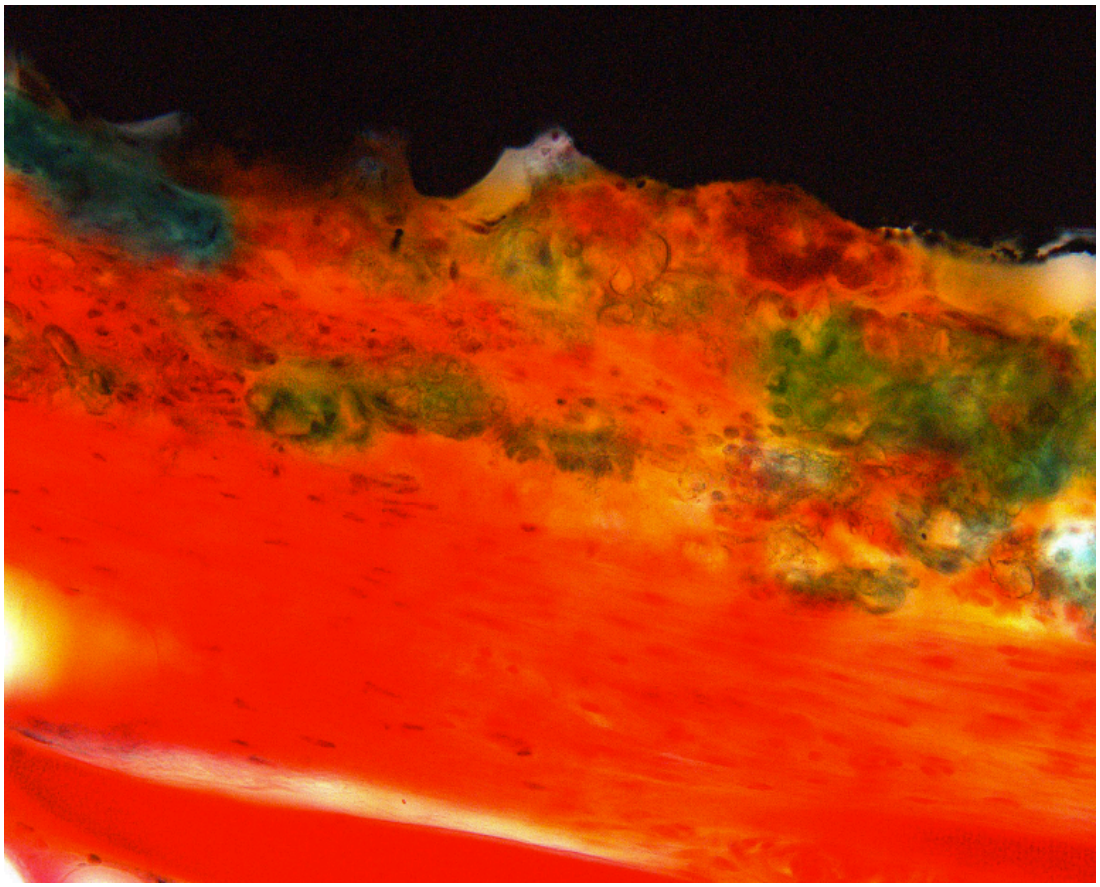

Figure 1. Light micrograph (primary magnification 40x) of implant with porous coating and plasma sprayed hydroxyapatite (PC + HA). Hydroxyapatite is stained green, however the coating is easy to distinguish from bone by its irregular structure. Titanium is seen as black in the top.

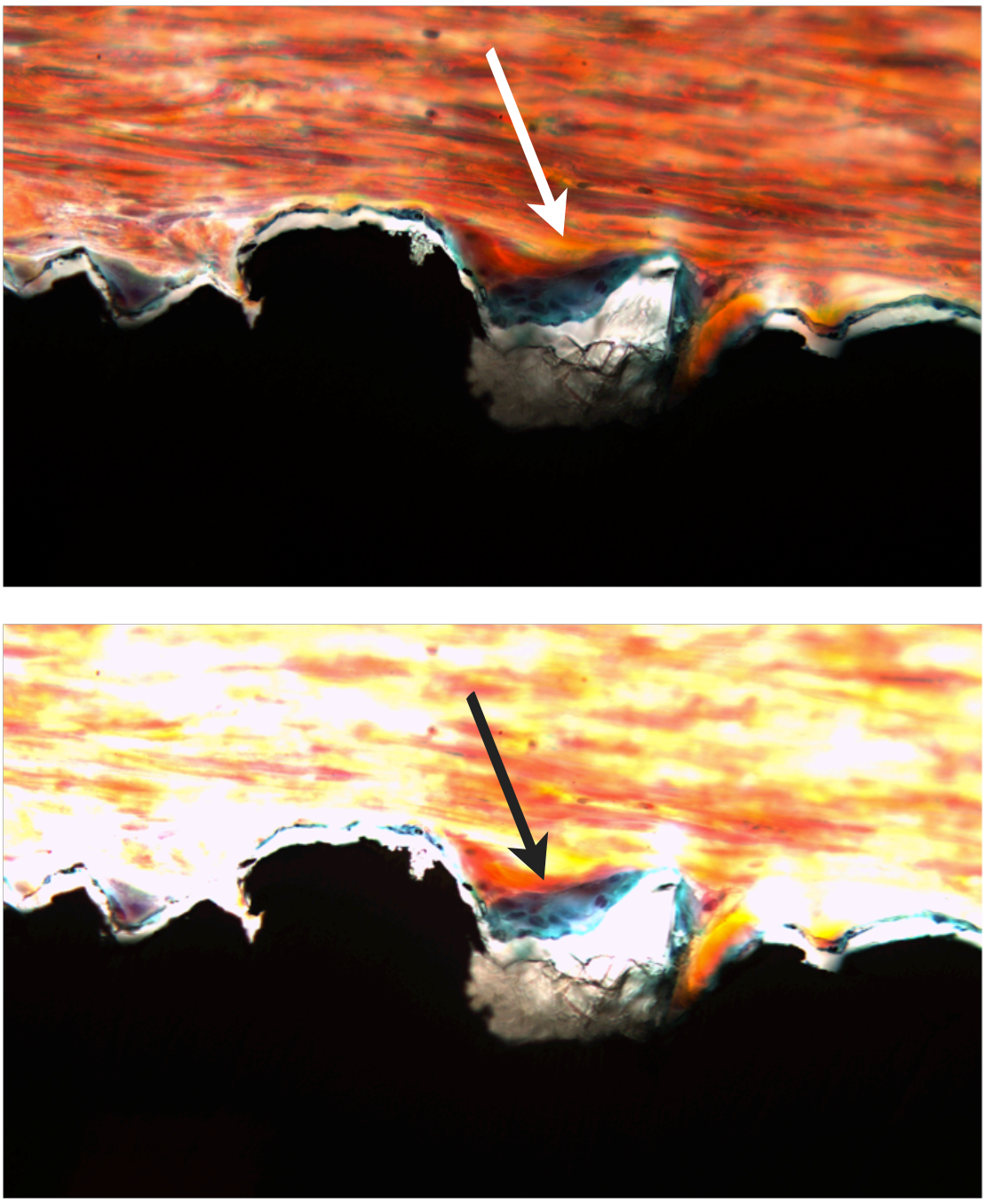

Figure 2 a and b. Light micrograph (primary magnification 40x) of bone formation seen as a thin green line along the implant surface (arrows). Same picture with different lightening. The implant is grit blasted with Bonemaster®.

Table 1. Bone induction around three of 4 different surfaces of titanium implants. The surfaces were grit blasted with Bonemaster® (GB+BM), porous coating (PC), porous coating with Bonemaster® (PC+BM) and porous coating with plasmasprayed Hydroxyapatite (PC+HA). Results after 6 weeks, 12 weeks and combined for 6 and 12 weeks together. p=0.02 with Fischer's exact test for 6 and 12 weeks together (STATA®).

	GB+BM	PC	PC+BM	PC+HA
6 weeks	2/6	2/6	1/6	0/6
12 weeks	2/5	3/6	0/6	0/6
Combined	4/11	5/12	1/12	0/12