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Sealing effect of hydroxyapatite coating

A 12-month study in canines

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ABSTRACT – This study addresses the clinical problems regarding access of wear debris to the bone-implant interface and the possible dissemination of polyethylene (PE) particles to distant organs. We inserted two implants into each knee of 7 dogs allowing access of joint fluid to the bone-implant interface with a 0.75 mm initial gap around the implant. Hydroxyapatite (HA)-coated and non-coated (Ti) titanium alloy implants were randomly allocated to each distal femoral condyle. PE particles were repeatedly injected into the right knee joint 3 weeks after surgery for a period of 49 weeks, while only vehicle was injected into the left knee joint.

We found huge amounts of PE particles mainly in the bone-implant interface around Ti implants. Infiltration of mononuclear inflammatory cells was present around 3 of 7 Ti implants in relation to PE particles. HA implants had approximately 70% bone ongrowth. In contrast, no bone ongrowth was seen on any Ti implants, all being surrounded by a fibrous membrane. The number of PE particles was evaluated semi-quantitatively. More PE particles were found around Ti implants than with HA implants ($p < 0.002$).

Specimens from iliac lymph nodes, liver, spleen and lung were examined and showed dissemination of PE particles only in regional lymph nodes.

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The mechanisms underlying aseptic loosening of joint prostheses have not been fully elucidated although they have been the subject of intense research during the last decades. The accesses of wear debris and joint fluid to the bone-implant interface probably play a crucial role (Schmalzried et al. 1992). However, it still remains uncertain what exactly initiates the failure.

Initial micromotion of the prosthesis has proven to be a good predictor of implant survival (Kärrholm et al. 1994b). Experimentally, micromotion alters the cellular response to wear debris by creating a more aggressive membrane around implants (Bechtold et al. 1995). Therefore it seems essential to obtain a stable interface sealed off from joint fluid containing wear debris and osteoclast-activating factors (Nivbrant et al. 1999). As regards non-cemented arthroplasty, experimental studies have shown promising effects of hydroxyapatite coating (Kraemer et al. 1995, Søballe et al. 1991, 1992, 1993a). Recently, we showed that HA coating after only 8 weeks effectively prevents the migration of polyethylene particles to the bone-implant interface (Rahbek et al. in press). We therefore suggested that this effect was due to early bone ongrowth. By achieving bony anchorage, initial implant stability was obtained

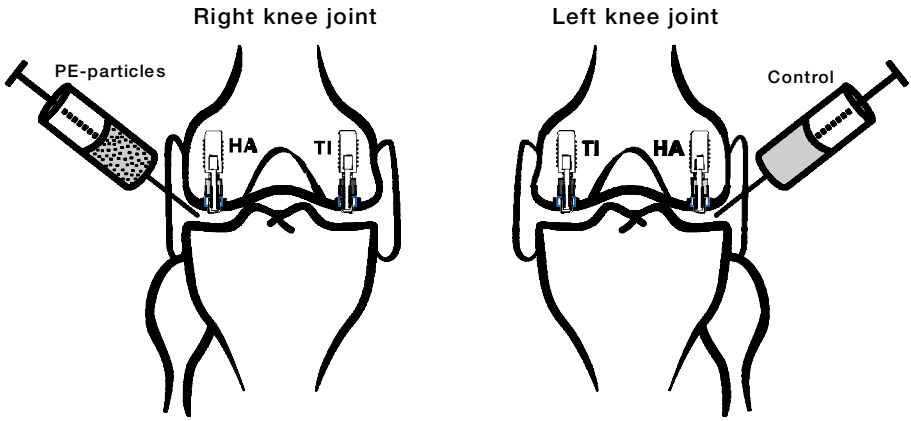

Figure 1. Design of the study. A HA-coated (HA) and a non-HA-coated implant (Ti) were randomly allocated to the medial or lateral condyle. If a HA-coated implant was allocated to the right lateral femoral condyle, a HA-coated implant was also placed in the lateral condyle in the contralateral knee. 3 weeks after surgery, high-density polyethylene particles dispersed in sterile hyaluronic acid were injected into the right knee joint. The left knee served as control and only hyaluronic acid was injected.

and "the effective joint space" was reduced. These results have raised questions about the long-term effects of HA coating.

The aim of the present study was to investigate the long-term effect of hydroxyapatite on peri-implant particle migration and bone-implant interface. Furthermore we studied the migration of particles to distant organs.

Animals and methods

Study design

7 mature mongrel dogs weighing 20–23 kg were used for this study. The dogs were bred for scientific purposes and were handled according to the Danish law on animal experimentation.

Loaded HA-coated and Ti implants were randomly allocated to each distal femoral condyle (Figure 1). The test implants were surrounded by a gap, which communicated with the joint space, and allowed access of joint fluid to the bone-implant interface (Figure 2).

Injection procedure. 3 weeks after surgery, we started weekly injections of 5 mL solution PE particles, dispersed in sterile hyaluronic acid, into the right knee joint (Figure 1). The left knee served as control and 5 mL hyaluronic acid without particles was injected. 8 weeks postoperatively, injections were given every 14th day using a double dose of particles. Injections were performed using sterile

Figure 2. Implant device and test implant positioned in the weight-bearing part of the femoral condyle. 1. Threaded anchorage screw fixed in bone. 2. Threaded piston, which is centered in the drilled hole by the anchorage screw. 3. Test implant mounted onto the piston. 4. Gap measuring 0.75 mm between implant surface and trabecular bone. 5. Titanium ring inserted into the subchondral part of the condyle to prevent early tissue ingrowth to the polyethylene plug. 6. Protrusion of the polyethylene plug (diameter 4.5 mm) which transmits the load from the tibial part of the knee to the implant system. Note the access of joint fluid to the peri-implant gap. Modified after Søballe et al. (1991), Søballe (1993).

technique during a brief intravenous anesthesia (methohexital). Parapatellar injections (2.5 mL each) were made into the lateral and medial joint chambers. The injections were repeated until the animals were killed 52 weeks after surgery.

Test implant characteristics. The implants were cylindrical (height 10 mm, diameter 6 mm), titanium alloy (Ti-6-Al-4V) implants with a grit-blasted surface. The HA coating was plasma-sprayed (thickness 50 μm, crystallinity 68% and purity 99%). The mean roughness (Ra) of the grit-blasted titanium surface was 1.12 (SD 0.04) μm and 1.25 (SD 0.05) μm for the HA-coated. The implants were sterilized by gamma irradiation.

Characteristics of injected material. The polyethylene powder consisted of 100% pure crystalline high-density polyethylene (HDPE) (information from manufacturer). The particle size distribution was determined by Scanning Electron Microscopy (SEM) (Cambridge S360, U.K.) with automatic image analyzing equipment. The analysis was performed at the Danish Technological Institute. The mean equivalence circle diameter was 2.09 (0.2–11) μm and the shape was spherical. The powder consisted of 7% particles, with a diameter less than 1 μm.

The particles were gamma-sterilized. Immediately before use, they were suspended in sterile hyaluronic acid (1.75 mg hyaluronic acid/mL phosphate-buffered saline, pH 7.4) and placed in an ultrasound bath for 30 minutes to homogenize the suspension. The suspension contained 5 mg HDPE (approximately 1.2×10^9 particles) per mL hyaluronic acid for the first 5 injections. The remaining suspensions contained 10 mg HDPE powder per mL hyaluronic acid. Particle dose was based on an estimated weekly production of 9.6×10^9 particles in a human total hip arthroplasty (McKellop et al. 1995). Assuming that the effective joint space in a human hip has a volume of approximately 45 mL, the weekly load was calculated to be 2×10^8 particles per mL. By injecting 6×10^9 particles per week into the knee joint of a dog (assumed volume 15 mL), we subjected the joint cavity to twice as high a load as in the human hip, namely 4×10^8 particles per mL joint.

Surgical methods

The implants were inserted with a sterile technique during general inhalatory anesthesia with halothane. An anterior parapatellar approach and medial arthrotomy were used. The vastus medialis and patella were dislocated laterally. To avoid thermal trauma to the bone, hand drilling was used to create a 7.5 mm hole, leaving a 0.75 mm gap around the implants. The cavity was cleaned from bone debris with physiological saline. After the anchorage screw was inserted, the implant and polyethylene plug were mounted onto the piston. The polyethylene plug protruded slightly above the cartilage, so a load was transferred through the implant system at each gait cycle. Prophylactic antibiotics (ampicillin) were administered immediately before and after surgery and analgesics (buprenorphine) were given daily for 6 days. Unstricted weight bearing was allowed postoperatively. The dogs were killed 52 weeks after surgery and the distal femora were immediately harvested. Bacterial cultures were taken from all the knees.

Biopsies from knee synovia, iliac lymph nodes, liver, spleen and lung were also obtained.

Specimen preparation

The distal femur, cleaned of soft tissue, was stored at –20 °C. Specimens were machined with a water-cooled diamond blade. Each bone-implant specimen was cut into halves parallel to the long axis of the implant in the frontal plane. By random one half remained undecalcified (Block A) and was dehydrated in graded ethanols (70–100%) containing basic fuchsin and embedded in methylmethacrylate. Then serial vertical sections were made with a newly-developed microtome (KDG-95, MeProTech, The Netherlands) at a distance of 350 μm between them (Baddeley et al. 1986). They were 25 μm thick and counterstained with 4% light green.

The other half was cut vertically through the middle of the implant in the sagittal plane and the implant was gently removed, without damaging the surrounding tissue. By random one part was stored in formaldehyde (Block B), decalcified (EDTA) and used to study particle migration along the implant interface and the cellular response. The remaining part (Block C) stored in 70% percent alcohol, pending analysis, is not included in this study.

Biopsies from synovia, iliac lymph nodes, liver, spleen and lung were embedded in paraffin and 7 μm-thick sections were stained with HE, Oil red O and for iron.

Histology

Undecalcified sections (Block A). A stereological software program was used (CAST-Grid, Olympus Denmark A/S) for histomorphometry. This is based on a user-specified grid applied on microscopic fields captured on the monitor (attached to a light microscope, objective ×10, ocular ×10). The vertical section method (Baddeley et al. 1986) and applied grid systems enabled us to calculate unbiased estimates using stereological methods by assuming no difference between lateral and medial specimen halves (Gundersen et al. 1988, Overgaard et al. 1998).

Ongrowth was defined as an implant surface covered by bone, bone marrow or fibrous tissue (in percent) and was estimated using the linear intercept technique. Approximately 245 (142–324) intersections in a mean of 5.6 (3–7) sections were counted per implant. Hereby the variance from the section level was reduced to a minimum (Overgaard et al. 2000).

Gap-healing was defined as percentage of the initial gap consisting of bone, bone marrow or fibrous tissue and was estimated using the point-counting technique (approximately 610 points on 4 sections per implant) (Overgaard et al. 2000). The initial gap area from the implant surface to 750 μm from the surface was analyzed.

EDTA-decalcified sections (Block B) and biopsies were fixed in 4% buffered formaldehyde and embedded in paraffin. Sections with a thickness of 7 μm were examined under polarized and conventional light microscopy to evaluate the presence of PE particles, the inflammatory response and iron deposits.

Migration of PE particles was evaluated with the integrated microscope-computer system, as described for the undecalcified sections using the same magnification. A counting frame (750 × 1100 μm) was applied on the computer screen. The initial gap was analyzed in a mean of 3.75 (2–4) sections per implant. A red-stained (ORO-stain) and birefringent dot or flake was defined as a PE particle. The number of PE particles inside the counting frame was graded according to Table 1. To evaluate the accuracy of the method, 54 sections from 14 implants were counted twice, and a coefficiency of variance on 6.7%, which was considered to be acceptable,was calculated.

Cellular response in the interface was evaluated blindly by two of the authors, of whom one is an experienced pathologist. The sections were graded semi-quantitatively with grades 0–3. Sections without mononuclear cells were graded as no inflammation and sections with mononuclear cells in a small area were graded as mild inflammation. Infiltration by mononuclear cells in more than one area of the section was graded as moderate and sections with chronic inflammation dominating the examined area were graded as severe (Table 2). Biopsies were graded in the same way. Marrow necrosis was graded as in Table 2.

Table 1. Grading system for polyethylene particle migration modified after Mirra et al. (1976) and Hicks et al. (1996)

Number of particles per counting frame	Grade
0	0
1–9	1
10–19	2
20–49	3
≥ 50	4

Table 2. Inflammatory response in bone-implant interface /marrow necrosis

	Right knee joint PE particles		Left knee joint control solution	
Dog	HA implant Ci/Mn	Ti implant Ci/Mn	HA implant Ci/Mn	Ti implant Ci/Mn
1	0/0	0/+	0/+	0/+
2	0/++	++/++	0/0	0/0
3	0/++	+/+++	0/0	0/0
4	0/++	0/0	0/++	0/0
5	0/0	0/x	0/0	0/0
6	0/+++	+++/++	0/0	0/0
7	0/0	0/0	0/0	0/0

Ci: chronic inflammation: 0 no, + mild, ++ moderate, +++ severe.
Mn: marrow necrosis: 0 no areas per section, + 1 area per section, ++ > 1 area per section, +++ marrow space dominated by necrosis.

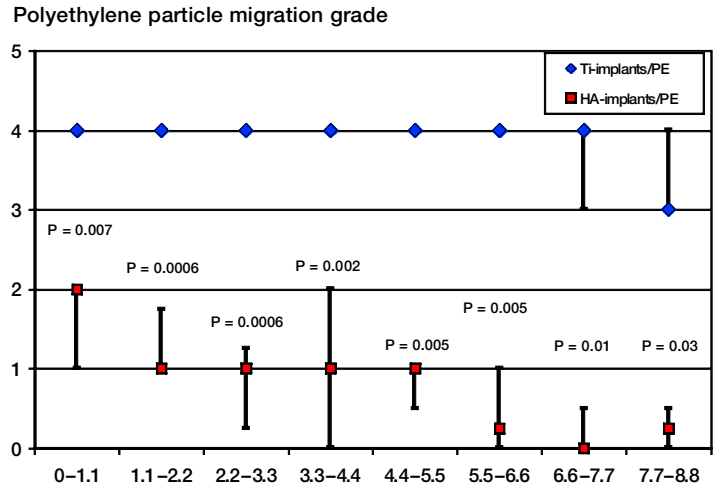

Figure 3. Median values (n 7) for polyethylene particles according to grading system (Table 1). Error bars = interquartile range. Data grouped in areas (1.1 x 0.75 mm) from the juxtaarticular tip of the implant. Presence of polyethylene particles was significantly reduced in all areas around HA coated implants. P-values are shown for each area.

Statistics

Data are presented as median values with range in brackets. Significance was determined by the Mann-Whitney rank sum or Wilcoxon's signed rank test. P-values less than 0.05 were considered significant.

Results

Migration of PE particles in the bone-implant interface

A marked difference in migration of PE particles between HA implants and Ti implants was found ($p = 0.001$), with median values of 1 (0–1.5) and 4 (1.5–4), respectively. Particles were scattered in the marrow space around HA coated implants. No particles were incorporated in bone. In the group of Ti implants, PE particles mainly occurred clusters in the peripheral part of the membrane. Small amounts of PE particles were found in interfaces around implants from the left knees. The particles were irregular in shape unlike the spherical shape of the particles injected into the right knee. This suggests that the PE plug in the implant system produced particles.

The pattern of migration in the interface differed between Ti- and HA-coated implants. Implants from the HA/PE group had significantly fewer particles in all zones than Ti/PE implants (Figure 3). In the group of Ti implants, equal numbers of particles were seen in all zones. In contrast, the number of particles in the juxtaarticular zone differed from that in the most proximal zone for HA-coated implants ($p = 0.001$).

Migration to distant organs

Histological examination of the right-sided medial iliac lymph nodes with polarized light and ORO staining revealed a large number of PE particles in both the cortical and medulla areas (Figure 4), but none on the left side. Biopsies from the spleen, lungs and liver showed no PE particles.

Morphology of bone-implant interfaces

Ti implants. A thin fibrous membrane with a lining of synovial-like cells surrounded all Ti implants. The layer beneath the synovial lining in the non-PE group was rich in extracellular matrix with fibers orientated parallel with the implant surface. In this layer, scattered spindle-shaped cells predominated. The deep layer of the membrane close to the bone had many capillaries and larger vessels. The membrane was, in most cases, bordered by a line of sclerotic bone. In the PE-injected group, an inflammatory reaction in the peri-implant membrane was found in 3 of 7 implants (Table 2). In those interfaces without inflammation,

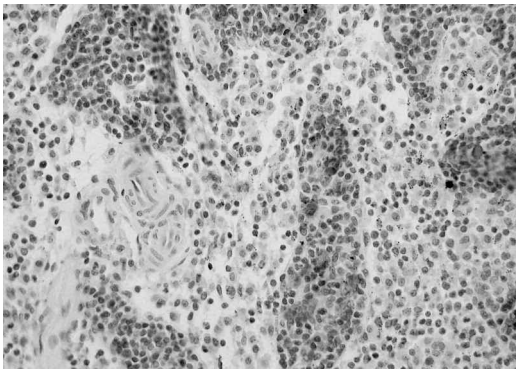

Figure 4. Histological section from right-sided lymph node showing cortical macrophages containing large amounts of PE particles, which are stained red (Oil red O stain) (×400).

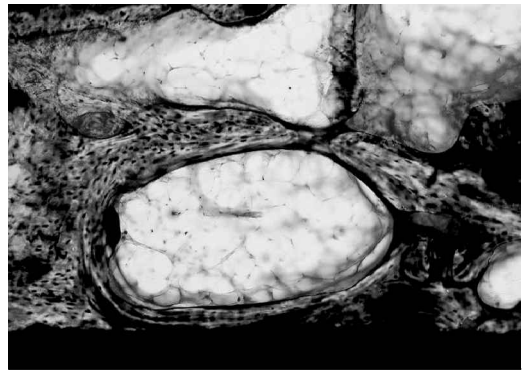

Figure 6. HA-coated implant with bone-implant interface. Undecalcified section stained with basic fuchsin and light green. Bone is green, soft tissue is red. The black object is the HA-coated implant (×100).

Figure 5. Histological section showing scattered PE particles in the membrane surrounding a Ti implant. Note the absence of a cellular response (Oil red O stain) (×200).

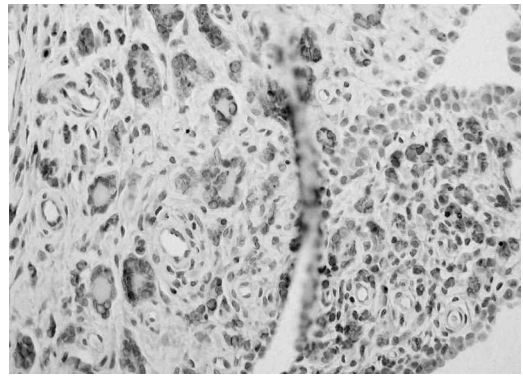

Figure 7. Histological section of a synovial biopsy. Several foreign body giant cells and macrophages containing PE particles. Note synovial thickening and chronic inflammatory response (×400).

the membrane resembled those from the control group, with the exception that the membranes contained large amounts of PE particles (Figure 5). The inflamed membranes were, in the worst case, dominated by many mononuclear cells with areas of necrosis. Lymphocytes, macrophages and plasma cells predominated. No foreign body giant cells could be seen in any of the sections.

HA implants. HA-coated implants were all surrounded by mature trabecular bone without synovial lining cells along the implant surface (Figure 6). No inflammatory reaction was seen around any implant. The difference in inflammation in peri-implant tissue between Ti implants and HA implants from PE-injected knees (Table 2) was not significant ($p = 0.3$)

Marrow necrosis. Examination of the bone marrow between implant and cortical bone revealed necrotic areas with a myxoid matrix in some specimens. No signs of inflammation were present around these areas and only a few PE particles were found around these lesions. There was no difference between PE-exposed and control groups for both HA and Ti implants separately ($p = 0.23$ and $p = 0.05$) (Table 2). If all implants were divided into two groups (n 14), a significant difference was found between the PE-exposed and control implants ($p = 0.03$), suggesting that the PE particles might be involved in the pathogenesis of marrow necrosis.

Synovial biopsies. Histological examination showed no signs of infection. In the particle-exposed knees, PE particles were located beneath the synovial lining cells along with lymphocytes and plasma cells. Inflammation was only present in the superficial part of the synovium. Multinu-

Table 3. Tissue ongrowth and gap-healing. The median values (range) are shown for bone and fibrous tissue in the four groups. HA implant = hydroxyapatite-coated implant, Ti implant = non-coated implant

	Right knee joint/PE particles		Left knee joint/control solution	
	HA implant	Ti implant	HA implant	Ti implant
Ongrowth (%)				
Bone	75 (27–79) [ab]	0 (0–5) [a]	71 (49–73) [b]	0 (0–1)
Fibrous tissue	0 (0–34) [ab]	100 (95–100) [b]	0 (0–6) [b]	100 (99–100)
Gap-healing (%)				
Bone	36 (27–42) [ac]	7 (0–40) [b]	38 (29–56) [c]	16 (5–31)
Fibrous tissue	0 (0–35) [ac]	86 (18–100) [a]	0 (0–12) [c]	81 (62–94)

[a] No significant difference, compared to control
[b] Significant difference, compared to unilateral Ti implant ($p < 0.02$)
[c] Significant difference, compared to unilateral Ti implant ($p < 0.03$)

cleated foreign body giant cells surrounded some of the particles (Figure 7). In the synovium from 2 dogs, a nodular infiltration of lymphocytes was found.

Histomorphometry

Ongrowth. HA implants had a bone coverage of 75% and 71% with no significant difference between HA-coated implants from the PE group and the control group (Table 3).

Areas with delamination of the hydroxyapatite coating were observed in 5 of 14 implants and 4% of the total implant surface was delaminated. Delaminated areas had ongrowth of 68% fibrous tissue, 16% bone and 16% bone marrow. If failure occurred in the juxtaarticular areas of the implant exposed to joint fluid, it was replaced by fibrous tissue, otherwise by bone tissue. The delaminated coating was, in most cases, well integrated in surrounding bone and did not induce a foreign body reaction.

Ti implants were almost completely surrounded by fibrous tissue and the presence of PE particles did not affect the tissue ongrowth.

Gap-healing. Exposure of PE particles did not affect the healing capacity of the initial gap around HA or Ti implants significantly. In the Ti implants the volume fraction of bone ranged from 0 to 40%. The two implants with the lowest values had the highest degree of inflammation in the interface. HA-coated implants had significantly more bone in the gap than Ti implants and had a low percentage of fibrous tissue (Table 3).

Discussion

Clinically, non-cemented hip arthroplasty with the use of HA coated stems and cups has shown promising results (Søballe et al. 1993b, Kärrholm et al. 1994a, Moilanen et al. 1996, Geesink and Hoefnagels 1997, Capello et al. 1998). Many surgeons prefer this technique for younger patients, although no one has proven that non-cemented implants have longer survival than cemented ones. In cemented arthroplasty, aseptic loosening is a matter of concern. The implant-cement interface and fatigue cracks in the cemented mantle are believed to provide pathways for wear debris to the bone-cement interface leading to localized bone lesions (Anthony et al. 1990, Crawford et al. 1999). Furthermore, particulate cement originating in the cement mantle is believed to contribute to peri-implant osteolysis (Horowitz and Gonzales 1996). Considering the problems with a cemented mechanical seal of the bone-implant interface, the possibility of a biological seal has been suggested (Kraemer et al. 1995). We define a biological seal as consisting of host tissue or other bio-active material, which can heal if defects occur due to mechanical stress. Thus, a more durable seal theoretically may be created. Kraemer et al. (1995) have, in a canine model, compared the ability of smooth, porous-coated, HA-coated and cemented hemiarthroplasties to prevent migration of PE particles. Sections from the distal tip of the prosthesis, from the mid-implant and from the proximal part of the prosthesis were examined. Particles

were found only in the sections from the smooth implants, which had ongrowth of fibrous tissue in all zones. Non-cemented technique with porous coating or HA coating and cemented technique were found to have an equal sealing effect on peri-implant PE particle migration with a complete sealing effect of the interface. Not even in the proximal zones, just below the beginning of the bone-implant interface, could any PE particles be detected with light microscopy. Bone ingrowth in proximal zones was 8%, 38% and 83% for smooth, porous-coated and HA-coated implants, respectively. No correlation was found between bone ingrowth and PE migration.

In the present study, we have used a model with controlled variables, which seems clinically relevant and, as it is loaded, the implant is inserted in trabecular bone and there is access of joint fluid to the bone-implant interface. The gap model was chosen, since cementless prostheses, although carefully inserted in a press fit, will have areas with gaps between the implant and the bone. These gaps may be regarded as an extension of "the effective joint space" (Schmalzried et al. 1992), and therefore as a potential pathway for migration of wear debris. This problem must be considered even greater at revision surgery of cemented arthroplasties or in patients with bone defects or osteopenic bone. To imitate the continuous production of wear debris in the clinical setting, we injected the particles at short intervals. The load of particles was doubled as compared with the estimated load in a human hip joint after arthroplasty (McKellop et al. 1995) and the dose was 24 times higher than the monthly load used by Kraemer et al. (1995). The load was increased to put a maximal stress on the interface. The clinical relevance of injecting a huge dose of particles 3 weeks after surgery can be discussed. In the clinical setting, it must be assumed that the wear rate initially is low and increases with patient activity. In the present study, we wanted to challenge implant surfaces by injecting a large amount of particles shortly after surgery.

Our results show that a HA coating can inhibit migration of PE particles in the bone-implant interface, as compared to grid-blasted Ti implants. We explain the sealing effect by the 75% bone ongrowth to HA-coated implants. Ti implants had no ongrowth of bone and were all surrounded by fibrous tissue, which yielded no protection against particle migration, in agreement with earlier findings (Bobyn et al. 1994, Rahbek et al. 1996). From the present study we can conclude that the bonding of bone to the HA coating does not decrease with time, in fact, it increases. We have earlier reported 35% bone ingrowth after 8 weeks (Rahbek et al. in press). These results might explain the clinical findings by Geesink and Hoefnagels (1997), where radiological results of HA-coated primary total hip replacement have shown an increase in bone mass around the prosthesis that was still improving 8 to 9 years after surgery. No patients with any mid- or distal stem osteolysis were seen, not even in those with extensive PE wear. These findings and the results o D'Antonio et al. (1996) support the long-term sealing effect of HA coating.

Many theories have been suggested about how wear debris mediates periprosthetic bone loss. Most research has focused on the secretion of osteolytic cytokines by macrophages, but there is increasing evidence that other cell types are influenced directly by the particulate debris. Submicron titanium alloy particles are thought to have cytotoxic properties, leading to tissue necrosis (Salvati et al. 1993, Pioletti et al. 1999). In the present study, we found more areas of marrow necrosis in the knees, which had been given injections of PE particles. However, we did not find large amounts of particles related to the necrosis. This could be due to the size of the particles, which induce cell necrosis. They could be only a few hundredths of a micron in size, and therefore not detected by light microscopy. The size of the injected PE particles was analyzed by SEM, but the detection limit of this analysis is 0.2 μm, so it remains unclear whether ultra-small particles have played a role in the pathogenesis. An alternative explanation could be that the marrow necrosis is mediated by inflammatory cytokines originating in the joint or interface. We did not find any occluded or dilated vessels, which could support a theory of infarction by the particles.

We detected inflammation only in some of the peri-implant membranes around Ti implants containing PE particles. The lack of a strong inflammatory response in the bone-implant interface to

the huge amount of PE particles could be related to the size or shape of the PE particles used. However, the size of the particles ranged from 0.2 to 10 and therefore contained submicron particles, which are primarily found around hip implants in vivo (Shanbhag et al. 1994, McKellop et al. 1995). Furthermore the particles had been phagocytosed by macrophages in the lymph nodes and, in the synovia, inflammation and foreign body giant cells were seen. Howie et al. (1988) first described PE particle-induced osteolysis in a stable bone-implant interface in an experimental study. A later study (Van Der Vis et al. 1997) using the same model, however, could not reproduce the original finding of osteolysis. It can therefore be speculated that other factors are necessary to mediate peri-implant inflammation and osteolysis. Recent findings suggest that it could be the combined effect of micromotion and particulate debris that causes the aggressive membrane around loose implants (Bechtold et al. 1995, 1996, 1997).

PE particles were found to migrate in large amounts in the lymphatic system, in agreement with clinical reports (Bos et al. 1990, Hicks et al. 1996), but were not detected in the liver, spleen or lung tissue. However, as previously mentioned, this does not exclude the presence of submicron particles. Metal particles from patients with arthroplasties have been demonstrated with electron microscopy and mass spectrometry in tissues such as bone marrow, spleen, liver, lung and kidney (Langkamer et al. 1992, Case et al. 1994). Widespread dissemination of wear debris should be taken seriously. Epidemiological studies have suggested a threefold risk of developing lymphoma and leukemia for patients 10 years after total joint replacement (Visuri and Koskenvuo, 1991, Gillespie et al. 1988). It has been suggested that the carcinogenic effect could be due to metal wear (Case et al. 1996). However, more recent studies have not confirmed the reports of an increased risk of leukemia or lymphoma for patients who have undergone joint implants (Gillespie et al. 1996).

Concerns have previously been raised about HA-coated implants (Bloebaum et al. 1994, 1997). Particulate debris originating from the HA coating are claimed to be able to induce an inflammatory reaction leading to osteolysis and third body wear. In our study, delaminated coating was in most cases integrated in the surrounding bone and we did not find any signs of inflammation around HA-coated implants. However, it must be stressed that the denuded areas had 68% ongrowth of fibrous tissue, which could serve as a potential pathway for wear debris. These results emphasize the importance of the quality of the coating and underlying surface texture (Overgaard et al. 1997), which is also important in the generation of third body wear (Bloebaum et al. 1997).

In conclusion, we found that the HA coating had a sealing effect on peri-implant migration of PE particles after 52 weeks due to osteoconductive properties. PE particles had no effect on bone ongrowth to the implants. The study indicates that chronic inflammation due to PE particles in the bone-implant interface might be inhibited by HA coating.

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Anthony P P, Gie G A, Howie C R, Ling R S. Localised endosteal bone lysis in relation to the femoral components of cemented total hip arthroplasties. J Bone Joint Surg (Br) 1990; 72: 971-9.

Baddeley A J, Gundersen H J, Cruz-Orive L M. Estimation of surface area from vertical sections. J Microsc 1986; 142: 259-76.

Bechtold J E, Søballe K, Lewis J L, Gustilo R B. The roles of implant motion and particulate polyethylene debris in the formation of an aggressive periprosthetic membrane. In Proceedings of the 41st Annual Meeting Orthopaedic Research Society, Orlando, Florida 1995.

Bechtold J E, Søballe K, Wang J Y, Tsukayama D T, Lewis J L, Gustilo R B. Cytokine release: Effects of implant stability, previous implantation, and bone graft. In Proceedings of the 42nd Annual Meeting Orthopaedic Research Society, Atlanta, Georgia 1996.

Bechtold J E, Søballe K, Kubic V, Overgaard S, Lewis J L, Gustilo R B. Synergy between implant motion and particulate polyethylene in the formation of an aggressive periprosthetic membrane. In Proceedings of the 43rd Annual Meeting Orthopaedic Research Society, San Francisco, California 1997.

Bloebaum R D, Beeks D, Dorr L D, Savory C G, DuPont J A, Hofmann A A. Complications with hydroxyapatite particulate separation in total hip arthroplasty. Clin Orthop 1994; 298: 19-26.

Bloebaum R D, Zou L, Bachus K N, Shea K G, Hofmann A A, Dunn H K. Analysis of particles in acetabular components from patients with osteolysis. Clin Orthop 1997; 338: 109-118.

Bobyn J D, Jacobs J J, Tanzer M, Urban R M, Aribindi R, Sumner D R, Turner T M, Brooks C E. The susceptibility of smooth implant surfaces to periimplant fibrosis and migration of polyethylene wear debris. Clin Orthop 1995; 311: 21-39.

Bos I, Johannisson R, Lohrs U, Lindner B, Seydel U. Comparative investigations of regional lymph nodes and pseudocapsules after implantation of joint endoprostheses. Pathol Res Pract 1990; 186: 707-16.

Capello W N, D'Antonio J A, Manley M T, Feinberg J R. Hydroxyapatite in total hip arthroplasty. Clinical results and critical issues. Clin Orthop 1998; 355: 200-11.

Case C P, Langkamer V G, James C, Palmer M R, Kemp A J, Heap P F. Solomon L. Widespread dissemination of metal debris from implants. J Bone Joint Surg (Br) 1994; 76: 701-12.

Case C P, Langkamer V G, Howell R T, Webb J, Standen G, Palmer M, Kemp A, Learmonth I D. Preliminary observations on possible premalignant changes in bone marrow adjacent to worn total hip arthroplasty implants. Clin Orthop (Suppl 329) 1996: 269-79.

Crawford R W, Evans E, Ling R S, Murray D W. Fluid flow around model femoral components of differing surface finishes. Acta Orthop Scand 1999; 70 (6): 589-95.

D'Antonio J A, Capello W N, Manley M T. Remodeling of bone around hydroxyapatite-coated femoral stems. J Bone Joint Surg (Am) 1996; 78: 1226-34.

Geesink R, Hoefnagels N. Eight years' results of HA-coated primary total hip replacement. Acta Orthop Belg (Suppl 1) 1997; 63: 72-5.

Gillespie W J, Henry D A, O'Connell D L, Kendrick S, Juszczak E, McInneny K, Derby L. Development of hematopoietic cancers after implantation of total joint replacement. Clin Orthop (Suppl 329) 1996: 290-6.

Gillespie W J, Frampton C M, Henderson R J, Ryan P M. The incidence of cancer following total hip replacement. J Bone Joint Surg (Br) 1998; 70: 539-42.

Gundersen H J, Bendtsen T F, Korbo L, Marcussen N, Møller A, Nielsen K, Nyengaard J R, Pakkenberg B, Sørensen F B, Vesterby A et al. Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. APMIS 1988; 96: 379-94.

Hicks D G, Judkins A R, Sickel J Z, Rosier R N, Puzas J E, O'Keefe R J. Granular histiocytosis of pelvic lymph nodes following total hip arthroplasty. The presence of wear debris, cytokine production, and immunologically-activated macrophages. J Bone Joint Surg (Am) 1996; 78: 482-96.

Horowitz S M, Gonzales J B. Inflammatory response to implant particulates in a macrophage/osteoblast coculture model. Calcif Tissue Int 1996; 59: 392-6.

Howie D W, Vernon Roberts B, Oakeshott R, Manthey B. A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles. J Bone Joint Surg (Am) 1988; 70: 257-63.

Kärrholm J, Malchau H, Snorrason F, Herberts P, Rorabeck C H, Bourne R B, Laupacis A, Feeny D, Wong C, Tugwell P, Leslie K, Bullas R. Micromotion of femoral stems in total hip arthroplasty. J Bone Joint Surg (Am) 1994a; 76: 156-64.

Kärrholm J, Borssen B, Löwenhielm G, Snorrason F. Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses. J Bone Joint Surg (Br) 1994b; 76: 912-7.

Kraemer W J, Maistrelli G L, Fornasier V, Binnington A, Zhao J F. Migration of polyethylene wear debris in hip arthroplasties: a canine model. J Appl Biomater 1995; 6: 225-30.

Langkamer V G, Case C P, Heap P, Taylor A, Collins C, Pearse M, Solomon L. Systemic distribution of wear debris after hip replacement. A cause for concern? J Bone Joint Surg (Br) 1992; 74: 831-9.

McKellop H A, Campbell P, Park S H, Schmalzried T P, Grigoris P, Amstutz H C, Sarmiento A. The origin of submicron polyethylene wear debris in total hip arthroplasty. Clin Orthop 1995; 311: 3-20.

Mirra J M, Amstutz H C, Matos M, Gold R. The pathology of the joint tissues and its clinical relevance in prosthesis failure. Clin Orthop 1976; 117: 221-40.

Moilanen T, Stocks G W, Freeman M A, Scott G, Goodier W D, Evans S J. Hydroxyapatite coating of an acetabular prosthesis. Effect on stability. J Bone Joint Surg (Br) 1996; 78: 200-5.

Nivbrant B, Karlsson K, Kärrholm J. Cytokine levels in synovial fluid from hips with well-functioning or loose prostheses. J Bone Joint Surg (Br) 1999; 81:163-6.

Overgaard S, Lind M, Rahbek O, Bünger C, Søballe K. Improved fixation of porous-coated versus grit-blasted surface texture of hydroxyapatite-coated implants in dogs. Acta Orthop Scand 1997; 68: 337-43.

Overgaard S, Lind M, Josephsen K, Maunsbach A, Bünger C, Søballe K. Resorption of hydroxyapatite and fluorapatite ceramic coatings on weight-bearing implants: A quantitative and morphological study in dogs. J Biomed Mater Res 1998; 39: 141-52.

Overgaard S, Søballe K, Jørgen H, Gundersen G. Efficiency of systematic sampling in histomorphometric bone research illustrated by hydroxyapatite-coated implants: optimizing the stereological vertical-section design. J Orthop Res 2000; 18: 313-21.

Pioletti D P, Takei H, Kwon S Y, Wood D, Sung K L. The cytotoxic effect of titanium particles phagocytosed by osteoblasts. J Biomed Mater Res 1999; 46: 399-407.

Rahbek O, Overgaard S, Søballe K, Bünger C. Hydroxyapatite coating might prevent peri-implant particle migration: a pilot study in dogs. Acta Orthop Scand 1996; 67: 58-9.

Rahbek O, Overgaard S, Bendix K, Lind M, Bünger C, Søballe K. Sealing effect of hydroxyapatite coating on peri-implant particle migration. Accepted by J Bone Joint Surg (Br).

Salvati E A, Betts F, Doty S B. Particulate metallic debris in cemented total hip arthroplasty. Clin Orthop 1993; 8: 160-73.

Schmalzried T P, Jasty M, Harris W H. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg (Am) 1992; 74: 849-63.

Shanbhag A S, Jacobs J J, Glant T T, Gilbert J L, Black J, Galante J O. Composition and morphology of wear debris in failed uncemented total hip replacement. J Bone Joint Surg (Br) 1994; 76: 60-7.

Søballe K. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs. Acta Orthop Scand (Suppl 255) 1993: 1-58.

Søballe K, Hansen E S, Brockstedt Rasmussen H, Hjortdal V E, Juhl G I, Pedersen C M, Hvid I, Bünger C. Gap healing enhanced by hydroxyapatite coating in dogs. Clin Orthop 1991; 272: 300-7.

Søballe K, Hansen E S, Rasmussen H B, Jørgensen P H, Bünger C. Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. J Orthop Res 1992; 10: 285-99.

Søballe K, Hansen E S, Brockstedt Rasmussen H, Bünger C. Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. J Bone Joint Surg (Br) 1993a; 75: 270-8.

Søballe K, Toksvig Larsen S, Gelineck J, Fruensgaard S, Hansen E S, Ryd L, Lucht U, Bünger C. Migration of hydroxyapatite-coated femoral prostheses. A roentgen stereophotogrammetric study. J Bone Joint Surg (Br) 1993b; 75: 681-7.

van der Vis H M, Marti R K, Tigchelaar W, Schuller H M, van Noorden C J. Benign cellular responses in rays to different wear particles in intraarticular and intramedullary environment. J Bone Joint Surg (Br) 1997; 79: 837-43.

Visuri T, Koskenvuo M. Cancer risk after Mckee-Farrar total hip replacement. Orthopedics 1991; 14: 137-42.